Victorian paediatric oncology care pathways

Providing optimal care for children and adolescents

Acute leukaemia and central nervous system tumours

June 2018

PICS
Victorian Paediatric Integrated Cancer Service

Victorian paediatric oncology care pathways: Providing optimal care for children and adolescents

Acute leukaemia and central nervous system tumours

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Foreword

Childhood cancer is by definition rare, and treatments are complex. Surveillance and follow-up are a lifelong process. Clinical management is characterised by the diversity of disease presentation, lead coordination by tertiary centres with higher case volumes, and the central role of clinical trials. The care experience is profoundly impacted by the patient's age, developmental stage and disease risk profile as well as the need for parents/guardians to act as decision makers.

Treatment and care for children diagnosed and treated for cancer is complex and challenging for all those involved. It involves multiple professionals and sometimes multiple services that may be close or distant to home. Best outcomes demand a timely, multidisciplinary, collaborative approach.

Documented cancer care pathways map the journey for specific disease/tumour types, aiming to foster an understanding of the whole pathway and its distinct components to promote quality cancer care and patient experiences. These pathways act as a reminder that the patient and family is the constant in the care continuum and that the health system has a responsibility to deliver the care experience in an appropriate and coordinated manner.

To be useful, a paediatric oncology care pathway needs to encompass the specific challenges of childhood cancer management. The Victorian Paediatric Integrated Cancer Service (PICS), supported by the Victorian Department of Health and Human Services, developed these oncology care pathways explicitly tailored for the care of children and adolescents. We acknowledge with gratitude the model provided in the adult cancer sector by the Optimal Care Pathways for Cancer Program, auspiced by the National Cancer Expert Reference Group.

The purpose of the paediatric oncology care pathways initiative is to improve children's outcomes by facilitating consistent cancer care based on a standardised pathway of care. The principles and the standards of good cancer care are not expected to differ from service to service, even though treatment regimens may vary from patient to patient for a variety of reasons.

A wide range of multidisciplinary clinicians and stakeholders in paediatric cancer were consulted or participated in the care pathway development including parent representatives. We want to thank all involved for their generous contributions. We are sure those providing paediatric cancer care will find the specific pathways useful in deciding how best to organise service delivery to achieve the best outcomes for those we care for. Importantly, readers should note that the pathway is not intended to constitute medical advice or replace clinical judgement.

The PICS is a partnership between the health services that deliver care and treatment to children and adolescents with cancer in Victoria. The paediatric oncology care pathways have been adopted by the PICS partners. Other jurisdictions are invited to adopt and co-badge these for their local use.

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Background

Paediatric oncology care pathways are intended to guide the delivery of consistent, high-quality, evidence-based care for patients with cancer. The pathways align with key service improvement priorities including providing access to coordinated multidisciplinary care and reducing unwarranted variation in practice.

The paediatric oncology care pathways are modelled on the adult Optimal Care Pathways developed by the Victorian Department of Health and Human Services and the Cancer Council Victoria (via the National Cancer Expert Reference Group). These are accessible at www.cancer.org.au/ocp

Each care pathway outlines seven critical steps:

1. Prevention and early detection
2. Presentation, initial investigations and referral
3. Diagnosis, staging and treatment planning
4. Treatment
5. Care after completing therapy and survivorship
6. Managing refractory disease or relapse
7. End-of-life care

Purpose

Oncology care pathways can be used by health services and professionals as a tool to identify gaps in current cancer services and to inform quality improvement initiatives across all aspects of the care pathway.[1] Clinicians can also use the pathways as an information resource and tool to promote discussion and collaboration between health professionals and families affected by cancer.[1] The pathway can also be very helpful for health professionals who may only have discrete involvement at one step in understanding the whole continuum of care.[2]

The paediatric oncology care pathways are also intended to provide a reference point for general practitioners (GPs) and paediatricians to guide decision making regarding referral to a paediatric cancer service and supporting shared care arrangements. They also provide guidance for the paediatric cancer service in the referral process to survivorship clinics and transition to adult healthcare.

This document is not intended to be a clinical practice guideline (CPG) and does not replace expert, multidisciplinary professional advice or clinical trial demands.

This document, dated June 2018, includes the Victorian paediatric oncology care pathway fundamentals of care, applicable to all tumour streams, and the oncology care pathways for acute leukaemia and central nervous system tumours. The solid tumours oncology care pathway is under development and will be added to this document once complete.

Scope

The paediatric oncology care pathways are intended as a resource in managing children and adolescents diagnosed with cancer from birth up to 18 years of age.

Critical time points

The blue clock symbol is used throughout this document to highlight a critical time point that has a specific timeframe attached to it.

A red clock symbol indicates the time point is part of an **urgent pathway**.

How to navigate the paediatric oncology care pathway

There are unique challenges in caring for children and adolescents with cancer that are distinct from the adult population. These include:

- the different disease types and prevalence
- the rarity and complexity of childhood cancer
- the impact of treatment on the developing child and the risk of significant late effects
- the increased role of clinical trials and need for international collaboration
- the family-centred versus patient-centred model of care.

The ‘fundamentals of care’ section covers key principles and fundamentals of paediatric oncology practice that underpin the care of all children and adolescents with cancer. Following that, disease/tumour specific pathways are outlined in separate sections. A summary is provided at the beginning of each disease/tumour specific pathway to highlight key aspects of each stage of care and emphasise critical time points.

SECTION 1:

PAEDIATRIC ONCOLOGY CARE PATHWAY — FUNDAMENTALS OF CARE

The ‘fundamentals of care’ section covers key principles and fundamentals of paediatric oncology practice that underpin the care of all children and adolescents with cancer. Following that, disease/tumour specific pathways are outlined in separate sections.

Why an oncology care pathway for children and adolescents with cancer?

- Cancer in children is rare and treatments are often complex.
- The types of childhood cancer differ greatly from those experienced in adults.
- Early diagnosis is important but can be challenging due to the rarity of the disease and diversity of presentations.

Safe and quality care

Health policy in Victoria is firmly anchored in principles of safety and quality. The State government has clearly outlined its vision for delivering better, safer care across the health system. The vision includes the following aspirations:[3]

- “World-class care patients receive is supported by a world-class system of quality and safety assurance
- Patient views and experiences are heard and shared at every point of the health system to drive continuous improvement
- Frontline healthcare workers have a real say on how to make the system safer and lead the way on improvement and best practice
- Individual safety and quality success is shared and built into the state-wide system”.

The Victorian paediatric oncology community shares this vision for better, safer care and recognises the adoption of care pathways as a tool for achieving service improvement.

Service capability — minimum standards

The paediatric oncology care pathways will be delivered by appropriately trained and credentialed clinicians within hospitals and health services that meet the minimum standards articulated in the Victorian Paediatric Integrated Cancer Service (PICS) documents:[4,5]

- *Service capability framework: a guide for Victorian health services providing primary treatment and shared care to children and adolescents with cancer* (2014)
- *Service capability framework: a guide for Victorian health services providing radiation therapy to children and adolescents with cancer* (2015).

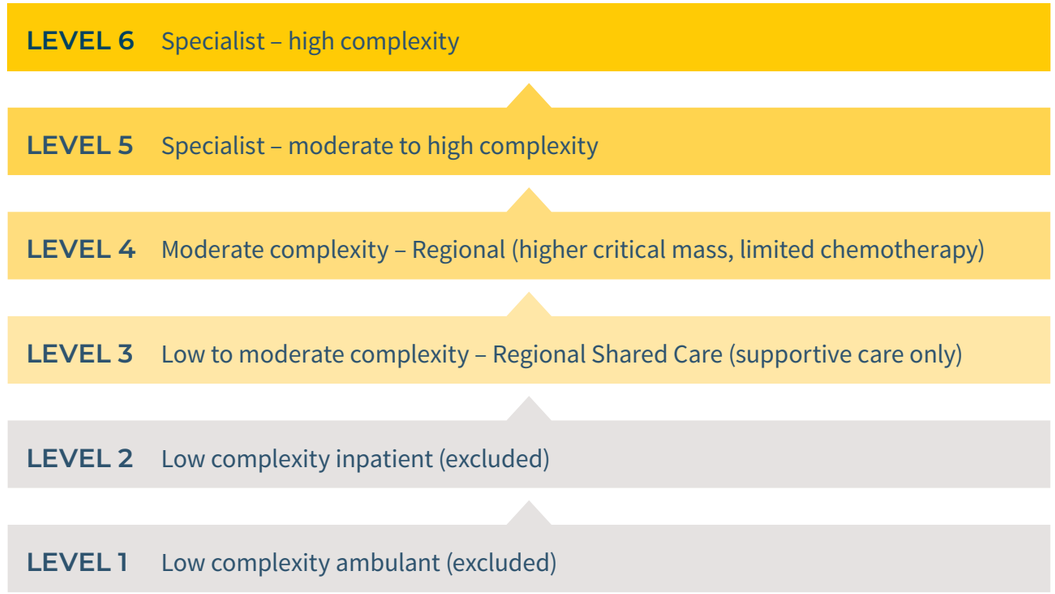
The objectives of these two frameworks are to:

- describe a coordinated system of state-wide paediatric oncology care
- support a sustainable model of care with efficient use of resources across health services
- support and advocate for patient safety through describing minimum recommended capability while providing care as close to home as possible
- provide clear and consistent language across state-wide services.

The emphasis of these frameworks is to define the minimum level of service capability required of health services across different time points in a child’s care. The frameworks support health services to plan, develop and deliver a high level of safe and effective paediatric cancer care within an agreed scope of practice. By documenting minimum requirements, health services will be assisted to deliver services that meet the local needs of the community and build confidence in shared care referrals between health services.

The *Service capability framework: a guide for Victorian health services providing primary treatment and shared care to children and adolescents with cancer*, identifies six paediatric cancer service levels, as outlined in Figure 1.

Figure 1: The levels of paediatric cancer services



The service capability frameworks are described in terms of the following dimensions:

- time points and level of complexity of care
- infrastructure
- speciality services
- workforce
- education and research
- quality and clinical governance
- service links and networks.

Whilst the frameworks define the minimum requirements for health services, this document builds on these requirements by defining optimal paediatric cancer care.

Principles of care

Family-centred care

In Australia, family-centred care is a philosophy of care endorsed by the paediatric healthcare community.[6,7] It has been defined across eight elements:[8]

- the family is central and constant in the child's life, while healthcare services change
- the facilitation of family-professional collaboration at all levels of healthcare, including program development, implementation and evaluation
- the exchange of complete and unbiased information between families and professionals, in a supportive manner
- recognition of cultural diversity across and within all families
- provision of developmental, educational, emotional, environmental and financial supports to meet the diverse needs of families
- encouragement of 'family-to-family' support and networking
- ensuring systems for children needing specialised care, and their families, are flexible, accessible and comprehensive
- the appreciation that children and families possess a wide range of strengths.

A family-centred care philosophy is required in the design, promotion, communication and delivery of all aspects of the care pathway for children and adolescents with cancer.

Multidisciplinary care

A centralised multidisciplinary approach to paediatric oncology care forms the basis of leading institutional recommendations[9,10,11] and has been demonstrated to improve patient outcomes.[12,13,14] The expertise within a disease-specific multidisciplinary team (MDT), usually located within a tertiary referral centre, is of particular importance in the field of paediatric cancer due to the rarity and complexity of management. The 'high-volume effect' within tertiary referral centres has been shown to improve survival outcomes in the paediatric oncology population.[15]

Multidisciplinary care is one of the key areas of reform for the Integrated Cancer Services in Victoria. Effective MDTs can support:

- improved treatment
- improved communication
- improved coordination of care
- improved access to clinical trials
- reduced service duplication
- better consideration of patient (and family) needs
- better promotion of shared learning and professional development.

- **It is a requirement that all children with a provisional cancer diagnosis be discussed at a paediatric oncology multidisciplinary meeting (MDM), with definitive diagnosis and prospective treatment planning forming the core themes.**
- **Core attendees of the MDM include all experts who are appropriate to the diagnosis.**
- **Documentation and dissemination of meeting outcomes are shared with key stakeholders including the family, the child or adolescent's GP and, if applicable, their paediatrician.**

Care coordination

Care coordination is a comprehensive approach to achieving continuity of care, ensuring that care is delivered in a logical, connected and timely manner to meet the needs of the patient.[1] In the context of a child or adolescent with cancer, this approach incorporates both the child and their family and includes MDMs, supportive care screening/assessment, referral practices, data collection, clinical trial participation, information provision and individual clinical treatment.

There should be a designated nurse within the MDT allocated to the child or adolescent with cancer with the responsibility to coordinate and communicate care.

Consistency of care

The primary oncologist should provide direct clinical consultation at all critical timepoints during the child or adolescent's treatment. These timepoints include:

- at diagnosis
- following investigations measuring response to treatment
- prior to each new cycle of treatment defined by the protocol
- following any significant morbidities
- at the end-of-treatment

and, if applicable:

- at relapse
- during the transition to treatment with a primarily palliative intent
- during the transition to end-of-life care
- during bereavement.

Communication

Communication with the child or adolescent with cancer and their family should be:[1]

- individualised
- candid and transparent
- consistent
- in plain language (avoiding complex medical terms and jargon)
- culturally sensitive
- active, interactive and proactive
- ongoing
- delivered in an appropriate setting and context
- offered in a variety of means such as printed and electronic media.

For the child or adolescent, information should also be tailored to their age and/or level of cognitive development. Medical play may support the needs of younger children, while opportunities for 'time alone' with the healthcare provider may benefit adolescents.

Place of care

Definitive diagnosis, staging/risk assessment and treatment planning for all children and adolescents aged 15 years or younger is made at a level five or six paediatric cancer service.

Adult health services managing patients with 'paediatric-type' cancers should have links to and advice from a level five or six paediatric cancer service and relevant MDTs.

Children and adolescents with 'adult-type' cancers should have links to and advice from an adult oncology service and relevant MDTs.

The child or adolescent's usual place of residence should be considered when determining the most suitable place of care. For patients living in outer metropolitan and regional areas, efforts should be made to support localised and home-based care when it is safe to do so.

Adolescent care

Adolescence is a time of considerable growth and development. These changes are characterised by physical, psychological, social, emotional and sexual maturational processes and can pose significant challenges.[16] The normal developmental process will be significantly harder for adolescents with a serious illness. Additional challenges include:

- difficulty fostering and maintaining peer relationships
- potential loss of autonomy and independence and the need for increased parental support
- sexual and reproductive health
- potential emerging mental illness
- education and vocation challenges
- the concept of assent and/or consent to treatment.

The health service needs to be cognisant of the needs of adolescents by:[17]

- ensuring access to expert adolescent health professionals with knowledge specific to the biomedical and psychosocial needs of the population
- understanding the biology and current management of the disease in adolescence
- considering clinical trials accessibility and recruitment for each patient
- engaging in proactive discussions and management of fertility optimisation and the late effects of treatment
- providing treatment in an adolescent and young adult (AYA) friendly environment
- acknowledging the importance of educational support in this age group
- fostering opportunities in adolescents for 'time alone' with health professionals where applicable
- promoting normality.

Transition from paediatric to adult care

Effective transition of adolescent survivors of cancer is an important part of the care continuum. As the incidence of late effects following treatment for childhood cancer has been shown to increase with age,[18] it is important that effective transition to adult care takes place to enable ongoing surveillance and earlier detection and intervention of late effects.

Challenges include the adolescent adhering to ongoing appointments when the focus of those appointments has moved from treatment to surveillance, often in a different healthcare setting[19] and with reduced parent involvement. Oncology services have limited involvement once the adolescent no longer has cancer. These patients may also require expertise from several specialties in the long term, making the transition more complex.

The model of care for transition will also depend on the availability of resources, the risk stratification of the individual and the complexity of care required. This means that some patients will remain in the tertiary adult healthcare sector rather than with their GP. Regardless of risk, a model that incorporates the patient's GP will reduce the potential for patients to be 'lost in transition' and is recommended.

Core principles for transitioning to survivorship programs should include the following:[20]

- the survivorship healthcare setting should be appropriate to the patient's age and cognitive development
- common concerns of young adulthood should be addressed in addition to speciality care. These include fertility, sexual health, contraception, self-management, psychosocial and emotional risk factors and access to healthcare[19]
- transition should promote autonomy, personal responsibility, self-reliance and a healthy lifestyle in young adults
- transition programs should be flexible to meet the changing needs of the young adult
- the process should be planned with the young adult and their family.

Fundamentals of paediatric oncology practice

Evidence-based practice — research and clinical trials

As the number of children and adolescents diagnosed with cancer is small, participation in collaborative international clinical trials is essential. This allows patients access to a wide range of trials and also enables the trials to recruit the critical mass of participants needed to deliver outcomes in the shortest possible timeframe. Outcomes may include improvement in overall survival or reduction in therapy, toxicities and/or late effects, as well as improved quality of life. Clinical trials may also enable access to off-label emerging therapies that would otherwise be unavailable to the clinician and patient. It is important to note that as more personalised, individual approaches to treatment increase the number of subpopulations of each disease, the already small disease population will become smaller.

- Eligibility for clinical trial enrolment should be considered for and offered to all children and adolescents diagnosed with cancer.
- For children who do not meet eligibility criteria, where enrolment is declined, or where a clinical trial is not open, the patient should follow the most recently completed and published 'standard of care' treatment protocol offering the best possible outcome (this may not be the current open trial).
- The cancer service should maintain a database of clinical trial enrolment for each diagnosis.
- Reasons why eligible patients are not enrolled and why patients come off study should be collated and any identified issues examined.

Trials in other disciplines in child and adolescent cancer care

Participation in clinical trials and research should be encouraged in areas other than primary treatment. These include:

- supportive care – for example, infection control and prevention strategies, palliative care, complications of therapy, nutrition, antiemetic control and fertility[21]
- epidemiology – for example, investigation of genetic causes to develop preventative measures[22]
- behavioural science – for example, neurocognitive batteries and assessment, identification of at-risk families and children, and psychological and behavioural interventions[23]
- nursing – for example, efficacy of patient and family education and reducing illness-related distress.[24]

Research and data collection

Other initiatives that should be encouraged include participation in a state-wide approach to trials and participation in national and international cancer registries and survivorship registries.

Supportive care

Supportive care is an umbrella term used to refer to services that may be required by those affected by cancer. Supportive care meets the needs across the following five domains:

- physical needs – for example, symptom management, managing and preventing infection, the impact of therapy on growth and development, physiotherapy, occupational therapy
- psychological needs – for example, the impact on cognition and education, managing stress and anxiety
- spiritual needs – for example, meaning-making in the context of illness
- social needs – for example, the child's access to their community, school and social networks
- information and communication needs of both the child and family.

Supportive care interventions in the paediatric context

Cancer affects the emotional, financial, social, physical and cognitive vulnerability of children and adolescents and their families.[25,26] Treatment of childhood cancer occurs in the context of a family and, as such, health services are required to ensure they meet the needs not only of the child or adolescent but of their family as well. This includes parents, siblings, guardians and care providers. Health services are required to provide access to appropriate information for parents and caregivers to effectively participate in treatment decisions with the healthcare team.

Risk groups

Patients and families that have a greater need for supportive care may include:

- infants
- children and adolescents receiving therapy for high-risk disease with significant toxicities from either therapies or underlying cancer
- children and adolescents who develop refractory disease or relapse
- children and adolescents with types of cancer for which there is no curative treatment available
- children and adolescents with pre-existing comorbidities
- single-parent and/or blended families

- families with mental health issues
- families with significant financial distress
- families where there are issues relating to child protection
- families from regional and remote areas
- families with cultural and linguistic diversity.

Supportive care assessments are shared with the MDT, documented and actioned at critical time points during and after treatment, including:

- at diagnosis
- following risk assessment
- during treatment
- at the end-of-treatment
- during the transition to survivorship
- during the transition to the adult healthcare sector
- at relapse
- during the transition to treatment with a primarily palliative intent
- during the transition to end-of-life care
- during bereavement.

Supportive care tools

Recommended tools for supportive care assessment are evidence-based, validated and age-appropriate. Tools may include:

- a validated psychosocial assessment tool for the patient and family (for example, PAT 2.0™)[27]
- a pre-chemotherapy nursing assessment tool (for example, SISOM or the memorial symptom assessment scale)[28]
- a performance status tool used prior to each treatment encounter (for example, the Karnofsky or Lanksy score)
- survivorship guidelines in assessing late complications of therapy (for example, the Children's Oncology Group survivorship guidelines)[29]
- a visual analogue score for chemotherapy-induced nausea and vomiting (for example, the BARF™ scale)
- a visual analogue score for pain assessment (for example, the FACES™ pain scale)
- validated tools for assessing mucositis in children and adolescents (for example, ChIMES)[30]
- a nutritional screening tool for children with cancer (for example, SCAN)[31]
- an AYA psychosocial screening tool (for example, HEADSS assessment).[32]

Clinical practice guidelines

The development and utilisation of CPGs in supportive care is essential to provide optimal care and reduce morbidity and treatment-related mortality.[33] Paediatric cancer services should ensure they are following evidence-based supportive care CPGs and should aim to promote national and international collaboration in their development.[33]

Neuropsychological demands

A risk algorithm for managing the neuropsychological effects of childhood cancer, and its treatment, is outlined in the PICS document *A compendium of evidence and framework for neuropsychological services in paediatric cancer (2015)*.[34]

This compendium was written with the aim to establish a risk algorithm using international guidelines and local data that could inform workforce requirements for neuropsychology services. It is recommended that health services use this framework.

Risk factors for neuropsychological morbidity in children include, but are not limited to:

- diagnosis of a central nervous system (CNS) tumour
- cranial irradiation (with higher intensities correlating with poorer outcomes)
- CNS-directed chemotherapy such as intrathecal chemotherapy
- chemotherapy agents such as high-dose methotrexate
- young age at diagnosis or during treatment
- co-existing neurocognitive morbidities
- perioperative complications related to neurosurgery.

Access to neuropsychology services should be risk-adapted and when required, be performed routinely at diagnosis and again at completion of therapy. Neuropsychology assessments should continue to be undertaken in survivorship.

Psychosocial standards of care

Psychosocial standards for paediatric oncology care are summarised below.[35]

- Patients and their families should receive routine psychosocial assessments.
- Patients in survivorship should receive yearly psychosocial screening.
- Patients and their families are at high risk of financial hardship, and targeted referral for supports should be made.
- Parents and carers are a psychosocially at-risk group and should have early and ongoing assessments.
- Siblings are an at-risk group and should be provided with appropriate supportive services.
- Patients and their parents should receive school re-entry and ongoing support to ensure the child remains on track academically.
- Patients should be provided with opportunities throughout treatment for social interaction.
- Patients and their families should be provided with psychoeducation, information and anticipatory guidance related to diagnosis, treatment and adaption.
- Patients should be referred to pain and palliative care services to reduce suffering throughout the disease process.
- A member of the healthcare team should provide bereavement management support following a child's death.

Every family should be seen by a social worker within one week of diagnosis.

A validated psychosocial screening tool is required to be completed at the time of diagnosis with the results (and ongoing actions) communicated to the MDT and documented in the patient's medical record.

Nutritional needs of children with a cancer diagnosis

For many childhood cancers, there is a risk of malnutrition during therapy.[36] In survivorship, there is a risk of obesity and developing metabolic syndrome.[37] These risks have the potential to be controlled with dietary and exercise interventions. Using a nutritional screening tool (both during and after treatment) can provide a way of identifying those patients at risk and offering early intervention.[31] Health services treating children and adolescents with cancer should adopt a validated tool for nutritional assessment as part of ongoing care during and after therapy, with referral to speciality services for those at risk.

Paediatric cancer services should give consideration for a nutritional assessment to be undertaken for all new diagnoses to guide the number and type of interventions required and further assessments during treatment.

All patients should have a nutritional assessment undertaken at each survivorship consultation.

Infection prevention and management

Infection is one of the most common complications in treating childhood cancer.

Recommendations for infection prevention and management in paediatric oncology are summarised below.

- Patients are required to undergo appropriate infection screening.
- Febrile neutropenia (FN) must be managed according to evidence-based guidelines.
- Families must receive information and education concerning the prevention and management of infection.
- Antimicrobial prophylaxis (viral and fungal) must be prescribed according to trial protocol or institutional guidelines.
- Household contacts should be up to date with vaccinations (including live vaccines).
- Annual influenza vaccinations should be provided to the patient and household contacts.
- The paediatric cancer service is required to demonstrate access to an infectious diseases consultant with experience in paediatric oncology.

In children with FN, antibiotics must be administered within one hour of presentation to hospital, or within 30 minutes for inpatients.

All patients should be identified as standard or high-risk of FN and be provided with documentation at diagnosis that identifies their risk category to streamline any required emergency care. This documentation should be updated according to the degree of perceived toxicity during each phase of treatment by a member of the MDT.

Palliative care

Palliative care needs should be assessed at all stages of a child's cancer diagnosis. Palliative care can be integrated into the child's management alongside disease-modifying therapy including chemotherapy, radiotherapy, bone marrow transplant and clinical trials. Specialists in palliative care are able to assist the oncology team with advance care planning, symptom management, spiritual care, psychosocial support, linking with community palliative care support services, end-of-life care and bereavement support.

Timely referral to palliative care support services promotes:

- the opportunity to focus on enhancing quality of life and reducing symptoms
- time to develop a tailored palliative care approach to the evolving needs of the individual child and family
- the avoidance of crisis-oriented management, which exacerbates the family's sense of vulnerability and helplessness
- a framework for preventive, proactive interventions and decision making
- support for the family's strengths and capacity to cope.

- When applicable, palliative care should be provided concurrently with active treatment.
- Palliative care should be integrated with care provided by the child's oncologist and other members of the MDT.
- Referral to palliative care support services should be considered in the context of:
  - high-risk diagnoses, where three- to five-year event survival is estimated at less than 30 per cent
  - high-risk disease or multiple relapses
  - disease progression on treatment
  - a history of prolonged (more than seven days) or multiple (three or more episodes in a six-month period) intensive care (ICU) admissions
  - patients without a curative therapeutic approach.

Fertility

Reduced fertility and infertility are potential consequences of many cancer treatments in children and adolescents and can result from:[38]

- exposure to selected systemic chemotherapy agents or radiation to reproductive organs
- high-dose radiation to the hypothalamic–pituitary axis, causing secondary hypogonadism
- selected pelvic, abdominal or neurosurgeries.

The potential for impaired fertility should be discussed and reinforced at different time points as appropriate throughout the diagnosis, treatment, surveillance and survivorship phases of care. These ongoing discussions will enable the family and, if applicable, the patient to make informed decisions.

Communicating fertility options

Discussing the impact of cancer treatment on fertility is an international standard of care. Infertility is acknowledged as a potential side effect of child and adolescent cancer treatment. Discussions should be standardised and follow institutional guidelines. If a procedure is deemed inappropriate due to medical risk or lack of efficacy in some patients, it is advised to have that discussion prior to treatment.

Communicating the options and potential risks to fertility should be discussed at diagnosis, coming off treatment and entry into the survivorship program.

Prevalence

Rates and degree of infertility vary greatly and are dependent on a number of risk factors, including the location of the disease, treatment regimen, treatment dose and pubertal status, which should be taken into consideration when discussing fertility options in children and adolescents with cancer.[39] Prediction of risk is difficult and outcomes vary amongst individual patients.

High-risk groups

The following interventions place young people at high-risk for infertility:[29]

- treatment with high-doses of alkylating agents such as cyclophosphamide, busulfan, ifosfamide, carmustine and procarbazine
- high-dose radiation to the pelvis, abdomen or hypothalamic axis, particularly in combination with alkylating agents
- total body irradiation for children and adolescents undergoing transplant conditioning
- testicular and ovarian radiation.

In discussing the late consequences of emerging therapies for childhood cancer such as immunotherapy, patients and families should be advised about the lack of conclusive data of the impact of these treatments on fertility, particularly in sperm production.

Education and information should include the enhanced risk of premature ovarian failure and/or early menopause faced by female survivors of childhood cancer.[40]

These different aspects of impaired fertility should be discussed and reinforced at different time points as appropriate throughout the diagnosis, treatment, surveillance and survivorship phases of care. These ongoing discussions will enable the family and, if applicable, the patient to instigate coping mechanisms and make informed decisions.

Fertility recommendations are outlined below. [41]

- An assessment of the risk of infertility is made by the MDT and documented at diagnosis for all patients.
- Families and, where appropriate, the child or adolescent, should be educated on the potential fertility-related effects of the treatment delivered.
- Discussions about fertility optimisation and why it may or may not be deemed appropriate should occur as early as clinically possible and prior to treatment commencing.
- Information should be provided in both verbal and written form regarding potential options, risks and benefits.
- Families who express an interest in fertility optimisation should be referred and, where clinically feasible, be seen by a fertility service.
- In those optimisation techniques where efficacy for future fertility cannot be adequately demonstrated, this should be clearly communicated to the child, adolescent and/or family.
- Families should be aware of the ongoing costs involved in fertility optimisation.
- All discussions should be documented in the patient's medical record.
- Clinical and ethical governance is required in centres offering fertility optimisation.
- Results regarding semen analyses and tissue biopsies should be communicated to the family as soon as possible, in case the potential for a secondary procedure is possible.
- Appropriate follow-up during treatment and survivorship is important to discuss results and legalities regarding tissue storage and to monitor reproductive function.

Complementary and alternative medicine in childhood cancer

Complementary and alternative medicine (CAM) refers to a diverse group of practices and products not considered part of evidence-based conventional medicine. CAM is not a substitute for conventional therapy and is not overseen by any health regulating body. In most situations, CAM is integrated into healthcare.

The ever-growing access to information has made parents, patients and families increasingly aware of CAM. How the role and potential benefits of CAM are presented in social media and online (often with limited objectivity) will drive an increase in its use. Caution must be used in supporting or advocating the use of CAM in children and adolescents with cancer, particularly the use of unproven medicines or supplements during therapy. This requires an open, effective relationship between the patient and the healthcare clinician.

The most common complementary health approaches used in children are:[42]

- dietary supplements (not including multivitamins)
- chiropractic or osteopathic interventions
- yoga
- deep breathing
- homeopathy
- meditation
- guided imagery
- massage
- special diets.

The main reasons cited for use of CAM in children and adolescents with cancer are to:[43]

- help fight/cure the child's cancer (with the concurrent use of conventional therapy)
- provide symptomatic relief
- support ongoing use of chemotherapy.

Some of the main reasons cited for CAM by adult cancer patients and their families are to:[44]

- improve physical and emotional wellbeing
- 'boost' the immune system
- reduce the side effects of conventional treatment
- improve quality of life.

- Patients should be encouraged to discuss all CAM with the treating team.
- Health services should have a policy governing the use of CAM.
- All discussions of CAM should be shared with the patient's oncologist and/or pharmacy and documented in the patient's medical file.

Genetic predisposition to cancer

Background

Common genetic variations are associated with a proportion of childhood cancers[45] and inherited genetic traits (germline mutations) currently account for about 10 per cent of all new diagnoses.[46] Many cancer predisposition genes continue to be discovered across adult and paediatric cancers[47] highlighting the need to develop specific services to address and provide reliable information about future risks faced by patients, as well as advice and strategies to lower the risk.

Genetic testing allows children and adolescents with a predisposition to developing cancer to be identified early. The potential clinical utility of identifying cancer predisposition genes in individual patients includes:

- providing an assessment on the likelihood of disease development
- altering treatment
- identifying targeted therapies
- using screening and prevention guidelines.

The number of patients with some underlying level of cancer predisposition is underestimated and under-reported. The addition of a genetic counsellor to the MDT has been shown to significantly increase the identification of such patients who could benefit from genetic evaluation.[48]

Genetic counselling, screening and prevention may greatly improve either the chance of avoiding the further onset of cancer or the outcome of the disease'.[46] However, health services need to also acknowledge the impact of results on the siblings and other family members, for example, where some germline mutations may be shared within the family.

Children and adolescents with cancer predisposition syndromes should be considered for referral to a genetic service.

- There should be access to a genetic service with experience in oncology.
- There should be access to a genetic counsellor in the health service with experience in oncology.
- All children with cancer should have a complete family history of cancer of at least three generations documented at diagnosis.
- The emerging family history of cancer should continue to be documented as part of the survivorship program, and consideration of referral to a genetic clinic where new family cancer histories in children or young adults are reported.
- The health service should have a management strategy that covers the ethical implications of genetic testing in other family members.
- The genetic clinic should continue to measure the efficacy and yield of findings of referrals to genetic services.

Coming off treatment

The coming off treatment and surveillance phase has been identified as one of the most difficult periods faced by parents in their child's treatment.[49] There are significant psychosocial and educational pressures encountered by patients and families during this critical time point.

Some of the major considerations for the cancer service to address with the patient and family coming off treatment include:

- education and learning requirements to be identified and tailored to the specifics of the child's cancer treatment
- that education requires the parent's readiness to learn during this point in care
- that the child's primary oncologist should remain responsible for managing cancer-related issues during the surveillance phase
- discussion with and assistance for the child/adolescent and parents in dealing with the fear of relapse
- education in differentiating significant from non-significant symptoms
- review of the initial diagnosis, the side effects and the follow-up care required
- review of any clinical trial requirements during surveillance
- interventions that meet educational and psychological needs of the child and adolescent not be delayed until referral to survivorship
- referral or reintroduction to psychosocial services.

- All patients should attend a formal, multidisciplinary end-of-treatment review.
- Every patient coming off treatment should be given a full summary of the diagnosis, staging, treatment received and any complications of treatment.
- Every patient should also receive a tailored surveillance roadmap. The roadmap should identify the recommended timings for clinical tests and investigations as well as referrals to the necessary support services. This should be tailor-made to the individual patient and cover the period from the end-of-treatment to entry into a survivorship program.
- Copies should be provided to the child/adolescent and their family, as well as their GP and paediatrician as appropriate.

Survivorship

Currently, more than 80 per cent of Australian children and adolescents diagnosed with childhood cancer will be cured. A substantial proportion will have adverse late effects requiring ongoing medical and psychosocial care.[50]
A system/service should be in place to support survivors of childhood cancer into adulthood and transition into adult healthcare services when necessary.

- All children and adolescents who have been treated for cancer or who have undergone an allogeneic stem cell transplant should be referred to a survivorship program.
- Patients in the survivorship program should follow an approach such as the Children's Oncology Group 2013 *Long-term follow-up guidelines* to ensure access to appropriate services.
- The survivorship program should undertake a risk-adapted approach to all patients entering the service for appropriate allocation of resources for those at higher risk of late effects.
- Paediatric oncology healthcare staff should be available, with access to clinical expertise and resources dependant on the child's risk and current guideline recommendations. This may include representation from areas such as cardiology, endocrinology, fertility, physiotherapy, nutrition, education, psychology, dental, social work, occupational therapy and rehabilitation.
- All patients should receive tailored educational material in a format appropriate to their level of understanding and language type.
- The summaries developed at the end-of-treatment must be updated with new information.
- The surveillance roadmap provided should be updated with new information on entry to the survivorship program, in line with current guidelines and recommendations. This should be made available to the patient and their GP and, if applicable, their paediatrician.

Relapse

Disease recurrence is a distressing experience as survivors and their families once again face the psychosocial effects of cancer: uncertainty, distress and concerns about death.

Treatment protocols for relapse can still provide a realistic chance of cure. However, in some diseases, the prognosis following relapse is poor. Relapsed treatment plans, by nature, are very distinct from the original treatment plan as the initial therapy has failed the patient. The treatment is generally more complex and intensive and the outcomes are more uncertain.[16]

Recommendations for patients with relapsed or refractory disease are summarised below.

- All patients with relapsed disease are required to be discussed at a paediatric oncology MDM to develop appropriate treatment planning, including decisions about potential clinical trial availability and possible referral to other specialty services including palliative care.
- The team should present all the information regarding the success rate of conventional relapse treatment plans, regardless of prognosis, and be available to discuss CAM options.
- The MDT should maintain open and candid communication at all times.
- Information is sensitively provided to the child/family, in plain language and in a supportive environment.
- There should be an increased focus on psychosocial support, including exploration of the family's strengths, a focus on enhancing quality of life, ongoing discussion within a multidisciplinary structure and an awareness of maladaptive behaviour, such as emotional or physical withdrawal and refusal to follow through with medical care.
- Due to the toxicities of many relapse protocols, referral to fertility services should be considered.

End-of-life care

The Victorian Department of Health and Human Services has developed the *Victoria's end of life and palliative care framework: A guide for high-quality end of life care for all Victorians*, available at www.health.vic.gov.au. There is also the National consensus statement on end-of-life care for paediatric patients developed by the Australian Commission on Safety and Quality in Health Care, which should guide practice in this area.[51]

Each child dealing with an incurable cancer will have different needs, priorities, goals and wishes as they approach the end of their life. The needs of their families will also differ. Supportive care interventions should aim to honour and facilitate the individual's preferences, which should be elicited with sensitive, open and candid communication.

Informational needs

Children with incurable cancer, and their families, have a high need for communication and support. Discussion regarding approaching end-of-life is likely to require an iterative approach and should be tailored to the individual and their family. Plain language should be encouraged, and euphemisms avoided. Discussions may encompass:[52]

- prognosis
- rationale for decisions to change the focus of therapy
- explanation of and plans for addressing and preventing symptoms
- referral to community palliative care support services
- advance care planning including place of care
- explanation of the dying process.

The family should be supported and encouraged to involve the child in discussions and decision making in a developmentally appropriate manner.

Symptom management

Symptoms at end-of-life should be vigorously managed using both pharmacological and non-pharmacological measures. This may include the use of palliative chemotherapy or radiotherapy.

Place of care

As the end-of-life phase approaches, clinicians should elicit the family's preferences for ongoing care and preferred place of death. Some families prefer to continue to have regular hospital visits for support. Others favour exclusive home-based care. Similarly, the choice between death at home, in hospice or in hospital is highly individual and may change as the disease evolves.

The dying process

Families should be guided in preparation for and recognition of the dying process. Signs of approaching death, including increasing fatigue, reduced conscious state, reduction in appetite and changes in temperature and breathing, should be described.

SECTION 2:

PAEDIATRIC ONCOLOGY CARE PATHWAY — ACUTE LEUKAEMIA

This oncology care pathway outlines seven critical steps for children diagnosed with acute leukaemia. While these steps are portrayed in a linear time model, in practice, patient care is rarely straightforward and predictable. The critical steps will require realignment and adjustment to best meet the needs of patients and their families as well as care providers without undermining the effectiveness of the treatment and supportive care program. The pathway describes the optimal cancer care that should be provided at each step.

The key principles and fundamentals of paediatric oncology practice outlined in the 'fundamentals of care' section underpin the oncology care pathway for acute leukaemia.

Scope

This oncology care pathway is intended as a resource in managing children and adolescents diagnosed with acute leukaemia.

Critical time points

As mentioned at the beginning of this document the blue clock symbol is used to highlight a critical time point that has a specific timeframe attached to it.

A red clock symbol indicates the time point is part of an **urgent pathway**. A precis of these time points are found in the summary of optimal timeframes (figure 3, page 24).

Summary

Figure 2: Paediatric oncology care pathway summary — acute leukaemia

Assess supportive and/or palliative care at every step of the pathway and refer to the appropriate health professional

STEP 1
Prevention and early detection

RISK FACTORS. There is currently no known cause of childhood leukaemia. There is a peak in incidence for acute lymphoblastic leukaemia (ALL) in early childhood and some genetic disorders increase the risk of developing leukaemia in childhood.

There is a link between developing acute myeloid leukaemia (AML) and prior chemotherapy exposure. There is no evidence that lifestyle plays a role in developing leukaemia. There are no preventative or screening programs for childhood leukaemia.

STEP 2
Presentation, initial investigations and referral

SIGNS AND SYMPTOMS. Clinical presentation is dependent on the level of leukaemic infiltration in the marrow and extramedullary sites at the time of presentation, resulting in a wide spectrum of signs and symptoms. Signs and symptoms that warrant a **full blood examination and peripheral film** include:

- a persistent unexplained fever
- diffuse bone pain with no obvious history of trauma and/or refusal to walk
- generalised lymphadenopathy
- pallor or unexplained bruising
- unexplained bleeding
- extreme fatigue
- recurrent respiratory tract infections.

Signs that warrant an **immediate referral to a paediatric tertiary referral centre** include:

- hepatosplenomegaly
- unexplained petechiae.

PARENTAL CONCERN. Escalation for further investigations is also warranted if there have been repeated GP visits or a high level of parental anxiety.

REFERRAL. All children and adolescents with a suspicion of leukaemia on clinical or laboratory grounds **will be discussed on the same day** with a level five or six paediatric cancer service.

Paediatric tertiary referral centres should provide clear routes of rapid access for GPs to specialist evaluation.

STEP 3
Diagnosis, staging and treatment planning

DIAGNOSIS. A diagnosis of leukaemia will require laboratory testing on both peripheral blood and bone marrow and include:

- assessment of morphology
- immunophenotyping, karyotyping and fluorescence in situ hybridisation (FISH) analysis
- molecular genetic analysis.

Tissue must be collected as a baseline at diagnosis to define markers that can be used for risk stratification, such as minimal residual disease (MRD) testing.

A lumbar puncture (LP) must be obtained at diagnosis to check for CNS disease.

TREATMENT PLANNING. Optimal treatment planning includes presentation to and consideration within **a paediatric leukaemia MDM** when all necessary tests and investigations have been completed.

CLINICAL TRIALS. Clinical trial enrolment should be offered to all children and adolescents with leukaemia. For patients who do not meet trial eligibility criteria, the most recent, evidence-based and published study protocol offering the best outcomes must be used.

COMMUNICATION. The lead clinician should discuss the outcomes of the MDM with the patient and family, including the diagnosis, risk assignment, treatment plan and access to clinical trials, if appropriate. The plan should be communicated with the GP and/or paediatrician.

STEP 4
Treatment

TREATMENT. Treatment protocols used must offer the best curative approach.

Chemotherapy is the key component of treatment, prescribed within validated treatment protocols.

Targeted therapies are also increasingly being utilised in leukaemia.

Radiotherapy. Any consideration for radiotherapy will be discussed within the paediatric leukaemia MDM.

Immunotherapy, including haematopoietic stem cell transplant (HSCT), may be required in some circumstances.

COMMUNICATION. The lead clinician should discuss the treatment protocol, including risks and benefits and supportive care measures, with the patient and family. The care plan should also be communicated with the GP and/or paediatrician.

Assess supportive and/or palliative care at every step of the pathway and refer to the appropriate health professional

STEP 5
Care after completing therapy and survivorship

COMING OFF TREATMENT. All patients will be provided with a surveillance roadmap covering the first three to five years after treatment.

SURVIVORSHIP. All patients completing treatment for childhood leukaemia will be referred to a survivorship program following surveillance.

Minimum documentation should include:

- a treatment summary
- a patient-specific roadmap for future tests and investigations.

TRANSITION OF CARE. Transition to adult care should be supported by the survivorship program or the cancer service, via a referral and documentation to the patient's GP. In selected patients having specialised therapies such as HSCT, referral to more specialty adult services may be warranted.

STEP 6
Managing refractory disease or relapse

DETECTION. Most instances of relapse or recurrence are identified through routine clinical examination or laboratory findings.

TREATMENT PLANNING. Optimal treatment planning requires presentation to and consideration within a paediatric leukaemia MDM. Early integration with palliative care should be considered.

TREATMENT. Children with relapsed ALL are often eligible for enrolment in clinical trials evaluating the effectiveness of chemotherapy alone, or in combinations of therapies including HSCT, chemotherapy and targeted therapies.

For patients with relapsed AML, treatment with chemotherapy may be an option, though chemotherapy followed by HSCT is currently the most common modality. Services should continue actively pursuing new treatment modalities for relapsed and refractory leukaemia such as targeted therapy and immunotherapy.

COMMUNICATION. The lead clinician should discuss the outcomes of the MDM with the patient and family, including treatment options, potential clinical trial enrolment, prognosis and risks and benefits of treatment. The plan should be communicated with the GP and/or paediatrician.

STEP 7
End-of-life care

PLANNING. Discussion should be held within the paediatric leukaemia MDM to determine those patients for whom no further disease-modifying therapy is warranted and to identify those approaching end-of-life.

COMMUNICATION of advance care planning, including preferred site of ongoing care and preferred location of death, must be undertaken with all families with primarily palliative goals of care. Referral to palliative care support services must be implemented, if not already undertaken. The plan should also be communicated with the GP and/or paediatrician.

Summary: Optimal timeframes

Figure 3 summarises the recommended timeframes across two pathways at critical time points in the management of acute leukaemia in children and adolescents. All other timings of care for treating acute leukaemia can be found within the document.

Urgent pathway: Some patients may present with oncological emergencies including, but not limited to, hyperleucocytosis, tumour lysis syndrome, mediastinal mass and coagulopathies. Urgent, same-day emergency assessment and diagnosis needs to be completed to allow rapid commencement of therapy to manage these emergencies.

Standard pathway: If the patient is stable and/or enrolled in a clinical trial, protocol requirements and institutional resources should guide timing for optimal diagnosis and treatment planning.

Figure 3: Recommended timeframes in managing acute leukaemia

STEP IN PATHWAY	CARE POINT	TIMEFRAME
Presentation, initial investigations and referral	**GP investigations and referral**	All children and adolescents with a suspicion of leukaemia on clinical or laboratory findings must be discussed on the same day with a paediatric tertiary referral centre and, if required, referred to a level five or six paediatric cancer service within 24 hours.
Diagnosis, staging and treatment planning	**Diagnostic interventions**	**Urgent:** Diagnostic investigations need to occur on the day of presentation **Standard:** Diagnostic investigations need to occur by the next business day in clinically stable patients; however, clinical trial requirements, as well as the level of institutional resources, should also guide timings.
	Central venous access	**Urgent:** Central venous access should be established on day of presentation when it is safe to do so **Standard:** A central venous access device should be placed prior to beginning intravenous chemotherapy.
	Multidisciplinary meeting	A referral for discussion at an MDM will be made within a week of diagnosis. Discussion at the MDM will also take place at the end of induction therapy.
Treatment	**Chemotherapy**	**Urgent:** Chemotherapy commenced on the day of presentation **Standard:** Chemotherapy commenced by the next business day in clinically stable patients; however, clinical trial requirements, as well as the level of institutional resources, should also guide timings.

STEP 1: Prevention and early detection

1.1 Prevention

Although risk factors have been identified, the cause of childhood leukaemia remains unknown.

There is no evidence that lifestyle plays a role in childhood leukaemia. It is important to ensure the patient and their family are aware of this to avoid feeling responsible for their child's illness.

1.2 Risk factors

Genetic predisposition

Some genetic disorders may increase the likelihood of developing leukaemia in childhood or adolescence. These include Down syndrome, neurofibromatosis type-1, ataxia telangiectasia[53,54] and Fanconi's anaemia.

Siblings

Siblings of children and adolescents with leukaemia have an increased risk compared with the general population, although the risk is still very low. In identical twins, the non-affected twin has an increased risk of developing leukaemia, occurring in approximately 15 per cent of cases when the first twin develops leukaemia between two and five years of age.[53] Generally when the second twin develops leukaemia, this occurs within six months of the first child.

Environmental factors

There is evidence to suggest that radiation exposure including from medical imaging sources, particularly during pregnancy and early childhood, may increase the risk of childhood cancer, including leukaemia.[55,56] However, the cumulative absolute risk is very small. Computed tomography (CT) scans in children and adolescents should be limited to situations where there is a definite clinical indication, with every scan using the lowest possible dose of radiation.[57] Other environmental factors, such as electromagnetic fields, parental smoking habits and paternal workplace exposures, have not been able to yield strong aetiological associations.[53]

There is a link between the use of chemotherapy (particularly topoisomerase-II inhibitors) for childhood malignancies and secondary leukaemia, particularly treatment-related AML.

1.3 Screening and early detection

There are no effective screening tools for detecting newly diagnosed leukaemia in children and adolescents. Most children present with an array of non-specific symptoms that prompt the parent or guardian to seek medical attention. These signs and symptoms can be quite varied and are listed below in step 2. Screening individual symptoms has been shown to have low positive predictive values for leukaemia in primary care.[58] Despite this, there is a need to educate GPs to appreciate the potential significance of these symptoms and make appropriate referral. Delays in diagnosis can adversely affect outcomes and have major implications on the acceptance of a cancer diagnosis and a patient and family's subsequent health-seeking behaviour.[58]

Children who have a higher predisposition to develop cancer, such as a genetic risk or previous treatment for cancer, should have regular medical consultations. Children with identified bone marrow failure syndromes should have annual bone marrow evaluations to identify potential leukaemia.[59]

STEP 2: Presentation, initial investigations and referral

Childhood cancer is rare. This represents a major diagnostic challenge for emergency departments and GPs.

This step outlines the process for establishing a provisional diagnosis and appropriate referral for a child or adolescent suspected of having leukaemia.

In isolation, alert symptoms do not have a strong positive predictive value but nevertheless should be used to guide early referral to a level five or six paediatric cancer service. One identifying factor that supports referral is repeated visits with the same symptoms but without a clear diagnosis. Similarly, parental 'insight' and anxiety should be a strongly noted and sufficient reason for referral.[6,60] This is in line with the National Institute for Health and Care Excellence's (NICE) recommendations.[9]

Specific 'alert symptom' guidelines should be encouraged in primary care to overcome the issue of rarity, including education for adolescents and parents and guardians.[9]

2.1 Presenting signs and symptoms

The clinical manifestations of leukaemia are dependent on the level of leukaemic infiltration into the marrow and extramedullary sites at the time of presentation, resulting in a wide spectrum of signs and symptoms. It is important to recognise parental concern; escalation for investigations should be warranted after repeated visits or high levels of parental anxiety.

- The following symptoms may warrant the consideration of a **full blood examination and peripheral film**: persistent unexplained fever, diffuse bone pain with no obvious trauma and/or refusal to walk, generalised lymphadenopathy, pallor, unexplained bruising, unexplained bleeding or extreme fatigue, persistent respiratory tract infections.
- The following signs warrant **immediate referral and presentation to a paediatric tertiary referral centre**: hepatosplenomegaly and/or unexplained petechiae.

2.2 Referral

All children and adolescents with a suspicion of leukaemia on clinical and/or laboratory findings will be discussed on the same day with a level five or six paediatric cancer service, and if required, referred to the service within 24 hours.

The GP should have a clear and timely process for paediatric referral.

The minimum documentation for referral should include:

- a referral letter, including the patient's demographics, relevant medical history, medications and allergies
- results of clinical investigations (including imaging and pathology reports)
- the need for interpreter services and other recognised significant psychosocial issues.

The GP should aim to provide electronic or printed confirmation of tests and investigations, but availability should not delay the referral or assessment.

STEP 3: Diagnosis, staging and treatment planning

Step 3 outlines the process for confirming the diagnosis, risk stratification and treatment planning of leukaemia in children and adolescents.

It is a requirement that all children and adolescents with leukaemia are managed by a level five or six paediatric cancer service.

Urgent pathway: Some patients may present with oncological emergencies including, but not limited to, hyperleucocytosis, tumour lysis syndrome, mediastinal mass and coagulopathies. For these patients, **urgent, same-day emergency assessment and diagnostic interventions** need to be completed to allow early commencement of therapy.

Standard pathway: diagnostic interventions should be planned for the next business day in clinically stable patients; however, clinical trial requirements, as well as the level of institutional resources, should also guide timings.

3.1 Diagnostic work-up and pre-treatment investigations

Physical examination and history

- A thorough physical examination and history is important to identify co-existing organ dysfunction and the extent of infiltration, such as the clinical effects of bone marrow disease and extent of extramedullary disease, as well as potential features of underlying genetic predispositions and pre-existing comorbidities.
- Once a diagnosis is confirmed, a comprehensive family cancer history of at least three generations' pedigree will help further identify patients and families with potential cancer predisposition or inherited syndromes.[54] This may in turn help guide treatment or provide support to the extended family.

A physical examination and history is required on the day of presentation to the level five or six paediatric cancer service.

Pre-treatment laboratory examinations

- Full blood examination and film review
- Urea and creatinine, electrolytes, liver function tests
- Uric acid and lactate dehydrogenase
- Blood group, antibody screen and red blood cell phenotype
- Coagulation studies

Pre-treatment medical imaging

A chest x-ray will provide evidence or confirmation of mediastinal masses, particularly in patients with T-cell ALL.

Pre-treatment investigations will be performed on the day of presentation to the level five or six paediatric cancer service.

Diagnostic laboratory investigations

Laboratory diagnostic work-up includes the following tests, performed on bone marrow and, at times, also on peripheral blood:[61]

- morphology
- immunophenotyping, karyotyping and FISH analysis
- molecular genetic analysis.

All diagnostic tests should be ordered in such a way as to reduce the number of investigative procedures requiring general anaesthesia, improve workflow and support clinical trial enrolment. One such example may be in the use of upfront flow cytometry on peripheral blood.

A LP is performed to establish whether there is any CNS disease. It is a requirement that the initial LP be performed with adequate platelet cover and performed by an experienced clinician to avoid trauma, and the subsequent need to deliver increased therapeutic lumbar punctures.

A bone marrow aspirate (BMA) and LP should be performed under a general anaesthetic.

Urgent pathway: For urgent cases, if it is safe to do so, the diagnostic BMA and LP should be performed on the day of presentation. Urgent patients include, but are not limited to, those who present with hyperleucocytosis, tumour lysis syndrome, mediastinal mass and coagulopathies.

Standard pathway: The diagnostic BMA and LP should be performed by the next business day; however, clinical trial requirements, as well as the level of institutional resources, should also guide timings.

Infection screening

It is important that infection screening is undertaken at diagnosis and prior to treatment. Screening should include:

- routine serology – HBV, HCV, HIV, HSV, VZV (for all patients prior to receiving blood products)
- EBV, CMV and toxoplasma (as indicated but particularly for patients that may require haematopoietic stem cell transplantation (HSCT))

For patients born or who have travelled overseas, particularly to tropical regions or tuberculosis endemic countries, consultation with infectious diseases must be sought.

Other investigations are as clinically indicated and on discussion with the infectious diseases service.

Infection screening should be performed prior to treatment, particularly prior to transfusion of blood products.

Comorbidities

Due to the toxicities of therapy, baseline organ function should be assessed at diagnosis. A thorough medical history will also help identify any pre-existing comorbidities.

Biobanking

Consent for biobanking of diagnostic material should be sought.[61] In many upfront clinical trials in leukaemia, biobanking is a prerequisite to enrolment.

Minimal residual disease (MRD)

A MRD level is a strong and independent predictor of relapse in childhood leukaemia and widely used for risk stratification.[62,63] This requires a diagnostic marrow or peripheral blood specimen to enable identification of leukaemia-specific markers.

MRD testing in childhood leukaemia should occur at the time points listed on the next page.[64]

For ALL:

- diagnostic (baseline MRD panel) specimen
- following induction therapy
- end of consolidation for those who are positive at end of induction
- following re-induction therapy in relapse
- prior to a transplant for relapsed patients proceeding HSCT.

For AML:

- diagnostic (baseline MRD panel) specimen
- end of the first course of induction
- consideration at end of subsequent course if positive at end of induction.

These time points will vary according to the protocol and may be overruled by clinical trial requirements.

Clinical trial investigations

Further laboratory tests may be required to enable enrolment onto clinical trials.

3.2 Staging and risk stratification

Stratifying risk according to evidence-based criteria ensures that patients at the highest risk of relapse receive appropriately intensified therapy while those with more favourable prognosis (the lowest risk of relapse) receive therapy of reduced intensity to reduce complications.

Risk stratification at diagnosis must be assessed by a current, internationally recognised, peer-reviewed classification tool.

Acute lymphoblastic leukaemia[60,65,66]

There are four main pillars that underpin risk stratification in ALL: host factors, disease presentation, disease biology and, most importantly, response to treatment.

ALL favourable prognosis:

- Host factors – for example, age older than one year and younger than 10 years
- Presentation – for example, peripheral white cell count at diagnosis of less than 50,000/µL
- Biology – for example, favourable genetic and biological features such as hyperdiploidy or ETV6-RUNX1 (TEL-AML1) positive
- Response – for example, negative MRD at the end of induction therapy.

ALL unfavourable prognosis:

- Host factors – for example, age younger than one year and older than 10 years
- Presentation – for example, peripheral white cell count greater than 50,000/µL at diagnosis, presence of extramedullary disease (CNS and testicular)
- Biology – for example, hypodiploidy and BCR/ABL
- Response – for example, positive MRD following first cycle of therapy.

Acute myeloid leukaemia[56,67,68]

Risk stratification in AML is primarily related to the disease biology and response to treatment.

AML favourable prognosis:

- Down syndrome-associated less than four years of age
- Acute promyelocytic leukaemia (these patients generally have translocation (15:17)
- Negative MRD at the end of induction chemotherapy
- Specific genetic and biological features such as translocation (8:21).

AML unfavourable prognosis:

- Extremely high or low body mass index at diagnosis
- Positive MRD at the end of induction therapy
- Specific genetic and biological features of the leukaemic blast cell such as FLT3 mutations and monosomy 5 and 7.

Application of new diagnostic techniques in the biology of childhood leukaemia continue to develop at a great pace.[69,65] The MDT needs to be aware of these changes and advances and ensure they are translated to the bedside.

3.3 The multidisciplinary team and treatment planning

Optimal treatment planning includes presentation at a paediatric leukaemia MDM.

It is a requirement that the MDT include all the experts required for the diagnosis and treatment planning of childhood leukaemia including:

- paediatric oncologist with a subspecialty in leukaemia*
- haematopathologist with experience and expertise in paediatric haematological malignancies*
- nurse consultant with experience and expertise in paediatric haematological malignancies*
- paediatric clinical trials coordinator
- paediatric oncology pharmacist
- paediatric infectious diseases consultant
- social worker with experience in paediatric oncology.

*Core members of the MDT who will be represented in person or remotely at the time of the meeting

Administrative support should also be sought for documentation and dissemination of meeting recommendations.

- Discussion at an MDM should occur within one week of diagnosis.
- All patients will be discussed at the MDM at the completion of induction therapy.
- All new diagnoses are reported to the state cancer registry.

3.4 Supportive care considerations

Supportive care demands in all children and adolescents with cancer is discussed in the 'fundamentals of care' section. The success in childhood leukaemia over the past 40 years has led to a stronger emphasis on health status and health-related quality of life. Enhancements in supportive care and better measures of short- and long-term health-related quality of life are essential and are increasingly being embedded into the primary aims of new leukaemia clinical trials.[70]

Supportive care requirements in the context of children and adolescents with leukaemia include:

- managing acute symptoms in newly diagnosed patients (including coagulopathies), providing blood product support and managing electrolyte abnormalities, including preventing tumour lysis syndrome
- managing other clinical symptoms at diagnosis due to extramedullary disease
- nutritional assessment at diagnosis and for all patients requiring HSCT as part of their treatment, though the risk of malnutrition in leukaemia in much less than in other types of childhood cancers[36] (there is a risk of obesity both during treatment and in survivorship)
- physiotherapy support in managing chemotherapy-induced peripheral neuropathy
- management and prevention of infection
- neuropsychology supports – referral to neuropsychology should be made for children who have experienced potential neurocognitive insult from triggers such as CNS-directed therapy (cranial radiation and intrathecal chemotherapy), those patients receiving high-dose methotrexate and patients who experience any significant CNS morbidity during treatment such as cerebral bleed, stroke, acute meningitis and encephalopathies
- consideration of palliative care referrals for patients with a high symptom burden.

3.5 Communication with the patient and family

Lack of access to information has been identified as a cause of stress and conflict with the healthcare team for families of children with cancer.[71] The family and patient (if appropriate) will be provided with both verbal and written information, specifically for consumers, on the following topics as a minimum:[72]

- diagnosis, treatment plan and prognosis
- management of fever and neutropenia
- side effects of treatment
- who/how to call their hospital and/or treating team
- clinical trials
- managing medications and compliance at home
- central line care

Continued next page

- caring for the child at home
- supportive care
- orientation to the hospital and overview of the healthcare team (key members)
- preventing infection
- blood counts
- follow-up appointments
- fertility optimisation options
- psychosocial issues.

Information specifically targeted to children with acute leukaemia immediately following diagnosis include:[72]

- neutropenia precautions
- medication adherence
- steroid side effects
- chemotherapy side effects
- bleeding precautions
- managing procedures
- nutrition
- anaemia.

Family education information is provided as part of the discharge plan following diagnosis.

Considerations must be made and strategies put in place for communicating with families with cultural and linguistic diversity, including providing access to interpreter services and translated educational materials.

Age and developmentally appropriate information should be available for children and adolescents.

The paediatric cancer service should be able to demonstrate a process for providing timely and consistent remote support and monitoring via the telephone for patients and their families at home.

STEP 4: Treatment

Step 4 outlines a framework for delivering treatment for leukaemia in children and adolescents.

Effective strategies to improve overall survival in childhood leukaemia are identified through international collaborative clinical trials.

4.1 Treatment intent

The intent at diagnosis for all children and adolescents with leukaemia is cure. Children who develop refractory or relapsed disease are discussed in step 6.

4.2 Timing of therapy

Urgent pathway: Treatment must begin on the day of presentation immediately following diagnostic interventions. Urgent patients include, but are not limited to, those who present with hyperleucocytosis, tumour lysis syndrome, mediastinal mass and coagulopathies.

Standard pathway: Treatment for leukaemia should commence by the next business day following diagnosis. In clinically stable patients, clinical trial requirements and the level of institutional resources available on the day to provide optimal care should guide timings.

4.3 After-hours admission of newly diagnosed patients

In some settings, paediatric patients admitted with newly diagnosed acute leukaemia on a weekend have been shown to have prolonged length of stay, increased time to chemotherapy and higher risk of organ failure.[73] The timing of diagnostic and therapeutic interventions should be flexible and reflect clinical need, particularly for patients who present with oncological emergencies.

4.4 The role of clinical trials and research in childhood leukaemia

The five-year overall survival rate in ALL for children and adolescents has increased to 92 per cent in 2013.[70] There has also been an improvement in AML survival, with current overall survival at 70 per cent.[74] In 1960 nearly all children with AML and ALL succumbed to their disease. To date, this dramatic reduction in mortality has largely been a result of collaborative research.[75]

The low incidence of childhood leukaemia in the general population requires active participation in national and international clinical trials to achieve statistically significant numbers for research.

Clinical trial enrolment should be offered to all children and adolescents with a leukaemia diagnosis where open trials are available. For children who do not meet eligibility criteria, or where a clinical trial is not open, the patient should be treated according to the most recent, evidence-based and completed study protocol (this may not be the current open trial).

Clinical trials for leukaemia are risk-stratified and coordinated and managed within international collaborative studies.

4.5 Chemotherapy

Chemotherapy is the key component for treating childhood leukaemia. Due to the complexity and toxicity of administering cytotoxic agents to children, adherence to medication safety standards (such as mini-bag vincristine infusions) and the demands for supportive care, intravenous chemotherapy should be delivered via a central venous access device.

Urgent pathway: Central venous access should be established on the day of presentation.

Standard pathway: Insertion of a CVAD should be undertaken prior to initial treatment.

- **Chemotherapy should be prescribed with the use of validated protocols within an electronic prescribing system.**
- **A documented procedure that is strictly followed on the prescribing, dispensing and administering of chemotherapy must be used.**

Minimum requirements for delivering chemotherapy are defined in the *Service capability framework: a guide for Victorian health services providing primary treatment and shared care to children and adolescents with cancer.*[4]

4.5.1 Treatment for acute lymphoblastic leukaemia (ALL)

Most treatments for patients with standard-risk leukaemia are delivered in the outpatient setting. At this point in time, treatment lasts between two and three years and is dependent on risk stratification.

Treatment (includes CNS directed therapy throughout)

TREATMENT (includes CNS directed therapy throughout)
INDUCTION Goal: Achieve rapid remission. Length: 4 weeks (high-risk period)
CONSOLIDATION Goal: Strengthen depth of remission and systemic treatment for sanctuary sites. Length: variable, weeks to months
DELAYED INTENSIFICATION Goal: Strengthened pulse of intense therapy. Length: 8–12 weeks (high-risk period)
MAINTENANCE THERAPY Goal: Provide a prolonged period of low-risk treatment to eliminate MRD. Length: 2–3 years

4.5.2 Treatment for acute myeloid leukaemia (AML)

All treatment for AML is intensive and is delivered within the inpatient setting. At this point in time, total duration is four to six months, dependant on risk stratification. Some children may progress to HSCT as part of the protocol.

TREATMENT (includes CNS-directed therapy throughout, cycles may be repeated)
INDUCTION I Goal: Achieve rapid remission. Length: 4 weeks
INDUCTION II Goal: Achieve rapid remission. Length: 4 weeks
CONSOLIDATION/INTENSIFICATION I Goal: Strengthen pulse of intense therapy. Length: 4 weeks
CONSOLIDATION/INTENSIFICATION I Goal: Strengthen pulse of intense therapy. Length: 4 weeks

4.5.3 Treatment for infant leukaemia

Infants diagnosed with ALL remain a high-risk subset with significantly inferior outcomes. Current event-free survival remains at 50 per cent, despite best-practice international collaborative trials.[70] Treatment is intensive and predominantly inpatient-based. New therapies are examining the addition of specific targeted therapies, as current treatment regimens have reached dose-limiting toxicities.[76]

It is important that infants with a leukaemia diagnosis are enrolled in clinical trials to provide optimal therapy.

4.5.4 Acute promyelocytic leukaemia (APML)

Although paediatric APML is rare, many children at diagnosis develop significant coagulopathy. Because of this, these patients are managed at diagnosis in the inpatient setting with ready access to intensive care. At this point in time, following induction, treatment is outpatient-based and specific to these patients, including the use of all-trans retinoic acid and arsenic trioxide.

4.5.5 Targeted therapy

The addition of tyrosine kinase inhibitors (a targeted therapy for specific high-risk subsets of ALL) has improved outcomes in recent international studies from a three-year survivorship of 35 per cent to 80 per cent.[70]

Cancer services should continue to search new targets in treating childhood leukaemia, particularly in the high-risk groups. Personalised medicine should stay within the framework of robust collaborative clinical trials.

4.6 Radiotherapy

The use of radiotherapy (RT) for CNS prophylaxis has been one of the most important advances in the treatment of leukaemia. Intrathecal prophylaxis and intensified systemic chemotherapy have now reduced the need for RT without any impact on long-term outcomes,[77,78,79] reducing the incidence of late neurological sequelae traditionally associated with cranial RT.

Currently, the use of cranial radiotherapy (CRT) in treating leukaemia is generally restricted to patients with overt CNS disease at diagnosis, and prophylaxis CRT is used in some patients with T-cell disease and other high-risk features. Internationally, protocols have drastically reduced the incidence of CRT and continue to do so.[79]

Radiotherapy also has a place in some patients for the treatment of testicular disease, salvage treatment in patients with isolated CNS relapse, as well as a part of the conditioning regimen for some children undergoing HSCT (total body irradiation). It can also be very useful in palliating symptomatic masses in advanced disease.

Patients receiving radiotherapy are usually treated outside of the level five or six paediatric cancer service. It is important that these patients are managed under the recommendations outlined in the *Service capability framework: a guide for Victorian health services providing radiation therapy to children and adolescents with cancer*, which describes the minimum service requirements for providing a coordinated, sustainable and consistent model of care for delivering radiotherapy to children and adolescents with cancer.[5]

Referral to radiotherapy services should be made once the treatment plan is confirmed.

4.7 Place of care

Treatment for childhood leukaemia is managed by a level five or six paediatric cancer service, in line with the *Service capability framework: a guide for health services providing primary treatment and shared care to children and adolescents with cancer.*[4] Consideration for supportive care and some aspects of treatment such as administering chemotherapy in shared care centres outside the level five or six paediatric cancer service should be made after consultation with the patient's MDT. Shared care centres are required to adhere to the standards outlined in the framework. Episodes of chemotherapy in regional shared care centres should be conducted with the use of telehealth between the local health service and the child's oncologist.

The child or adolescent's usual place of residence should also be considered when determining the most suitable place of care. For children living in outer metropolitan and regional areas, efforts should be made to support localised and home-based care, when it is safe to do so.

At a time when cure is agreed not to be the primary goal of care, the child and family's preferences for site of ongoing care and site of end-of-life care should be explored.

4.8 Managing and preventing infection

Treatment-related mortality in AML in children and adolescents has been shown to be as high as 10 per cent.[74] Time to antibiotics greater than one hour in managing FN in high-risk groups has been shown to have negative outcomes in paediatric studies.[80,81] Children and adolescents with Down Syndrome ALL are also at increased risk of treatment-related mortality and morbidity.[82] In addition to the infection recommendations in the 'fundamentals of care' section, strategies to mitigate infection risk in children or adolescents with leukaemia are identified below.

- Mandatory hospitalisation should be considered for all patients with AML and those patients with Down Syndrome-ALL during induction and periods of neutropenia.
- Consideration for hospitalisation during induction for non Down Syndrome-ALL should be made based on clinical and social/ compliance factors.
- Patients undergoing HSCT or treatment for AML must be treated in facilities appropriate to provide sufficient isolation from airborne pathogens, particularly fungal disease (such as HEPA filtration and positive pressure rooms).
- Strategies and policies should be in place for the management of infectious patients within the oncology clinical environment and waiting areas.
- For patients with FN, antibiotics must be administered within an hour of presentation to hospital, or within 30 minutes for inpatients.
- Patients with AML/ALL during the induction and intensification phases of treatment or those immediately (+ 30 days) post HSCT are at high-risk of sepsis. They must be identified as such and follow a high-risk pathway for FN.

4.9 Role of haematopoietic stem cell transplantation and other cell therapies

HSCT is an established treatment regimen for haematological malignancies in children. HSCT should be considered in selected patients at greatest risk of relapse where there is evidence that this modality improves outcome. As the understanding of the biology of leukaemia and treatment with chemotherapy and targeted therapy has improved, the indication for HSCT has reduced. HSCT is more widely used as a salvage where primary treatment has failed.

4.9.1 Indications for haematopoietic stem cell transplantation in leukaemia

The indications for HSCT in leukaemia should be reassessed continuously by the cancer service.[83] At this point in time, consideration for HSCT may include:

- ALL with high-risk features, for example, t(4:11), hypodiploidy and/or induction failure
- AML patients with high-risk features
- Mixed-phenotype acute leukaemia
- infant leukaemia with poor prognostic criteria
- relapse during or shortly after first remission
- persistent positive minimal residual disease.

All patients being considered for HSCT will be discussed at a leukaemia MDM.

4.10 Adherence and compliance to treatment for leukaemia

Treatment for childhood leukaemia can be up to three and a half years, with much of the treatment (oral chemotherapy) delivered in the home. The rate of medication errors in the home for children with cancer have been shown to be very high.[84,85] Non-adherence to oral chemotherapy in ALL has been demonstrated to occur due to practised restrictions placed upon families.[86] Cancer services are required to demonstrate strategies to support patients, families and caregivers in adhering to the treatment plan, particularly the role of long-term oral chemotherapy in the home.

The cancer service should have in place a mechanism to measure and record compliance with home-based oral medication administration, including how changes to oral chemotherapy doses are communicated to families in both written and verbal forms.

Step 5: Care after completing therapy and survivorship

5.1 Coming off treatment and surveillance in leukaemia

All patients are required to attend an end-of-treatment consultation following completion of treatment for leukaemia. This should be a multidisciplinary episode of care, including their primary oncologist, nurse consultant (with expertise in managing childhood leukaemia) and, if enrolled in a clinical trial, their study coordinator.

A referral to a survivorship program should occur at completion of treatment with the view of transition to the survivorship program at the completion of surveillance.

All patients with a leukaemia diagnosis should be provided with a treatment summary, surveillance roadmap and educational material specific to coming off treatment at their end-of-treatment consultation. The summary should also be sent to the child's GP and if applicable to the paediatrician.

The surveillance roadmap is sourced from the study protocol delivered for that individual disease and should be strictly followed, regardless of clinical trial enrolment. This roadmap should be prepared in collaboration with the survivorship program.

Surveillance includes:

- full blood examination and peripheral film
- Alanine Aminotransferase (ALT) and Urea, Electrolytes and Creatinine (UEC) testing on blood until normal recovery
- physical examination and history.

Echocardiograms will be undertaken routinely during surveillance for patients treated with chemotherapy for AML and ALL, as defined by the clinical trial protocol.

Planned episodes of surveillance following treatment for leukaemia are, at a minimum:

- first year – every four to six weeks
- second year – every eight weeks
- third year – every 12 weeks
- fourth year – every six months.

For patients enrolled on clinical trials, timings will be determined by the study protocol.

The length of surveillance for leukaemia usually lasts between three and five years. The medical management during the surveillance period should be directed by the primary paediatric oncologist. However, if provided with the adequate information and escalation criteria, consideration of the GP or paediatrician undertaking a portion of this under a shared care arrangement should be considered. Families from regional centres should be encouraged to conduct reviews under a telehealth model with the regional healthcare team, as deemed appropriate by the MDT. The demands for managing children enrolled in a clinical trial should be met prior to shared care being discussed.

5.2 Haematopoietic stem cell transplant

Children and adolescents who received a HSCT as part of therapy for leukaemia should follow a specific evidence-based surveillance roadmap, including routine bone marrow evaluation, designed by the transplant team, tailored to the patient's level of immunocompetence.

5.3 Survivorship

All patients who have been treated for leukaemia should be referred to a survivorship program at the completion of treatment with the view of transition to the survivorship program at the completion of surveillance.

All patients who have been treated for leukaemia should be participating in a survivorship program from three to five years after completing treatment.

All patients should be given an updated treatment summary and a roadmap for late effects surveillance on entering the survivorship program.

Patients and their families should also be provided with educational material about survivorship, including adopting a healthy lifestyle.

Large cohort studies show there is a low prevalence for significant adverse long-term outcomes in ALL and recommend regular, primary care consultations.[87]

Late complications specifically related to childhood leukaemia may include:

- deficits in neurocognitive functioning, particularly with CNS-directed therapy
- impaired cardiac function due to the use of anthracycline chemotherapy
- neuropathy
- risk of obesity and metabolic syndrome, particularly in those patients treated with cranial radiation.

Increased support in survivorship is necessary for children with AML, particularly due to the risk of cardiotoxicity, secondary to the use of anthracyclines.

Increased surveillance and monitoring is also necessary for those who have undergone a transplant due to the increased toxicities of therapy, particularly during conditioning and any graft versus host disease.

See the 'fundamentals of care' section under 'survivorship' for more information.

5.4 Transition from paediatric to adult care

Most survivors of childhood leukaemia will be transitioned to a GP with a treatment summary and roadmap outlining investigations and surveillance required. For patients who have undergone a transplant, transition to an adult transplantation service may be appropriate. See the 'fundamentals of care' section for more information on transition.

STEP 6: Managing refractory disease or relapse

Despite approximately 90 per cent of children with ALL being cured of their disease, relapse remains the most common cause of treatment failure, occurring in 15–20 per cent of all patients.[88] Of those children who relapse, cure only occurs in about 50 per cent of patients.[89]

In AML, 30 per cent of all patients will relapse, and recent studies show only 30–40 per cent of those patients survive.[90]

6.1 Signs and symptoms

Most cases of disease recurrence or relapse are identified through routine investigations or follow-up. Relapse may be discovered by peripheral blood examination (ordered during or after treatment) or via routine examination of bone marrow at critical time points during the child's treatment. Extramedullary relapse may be made during physical examination (such as testicular relapse or hepatosplenomegaly) or via routine cerebrospinal fluid examination during therapy.

Factors contributing to prognosis in relapsed ALL include:[16]

- marrow relapse less than three years from diagnosis (poor)
- extramedullary relapse (for example, CNS) less than 18 months from diagnosis (poor)
- marrow relapse longer than three years since diagnosis (favourable)
- extramedullary relapse longer than 18 months since diagnosis (favourable)
- response to initial therapy.

In AML, the length of time from the first remission is a major predictor of survival (with longer periods more favourable).

6.2 Multidisciplinary team

There should be an immediate referral to a leukaemia MDT at a level five or six paediatric cancer service for all children with suspected or confirmed relapse.

6.3 Treatment

Children with relapsed ALL are often eligible for enrolment in relapsed protocols, often involving the delivery of systemic chemotherapy and the use of HSCT for selected patients. Transplant remains an option in relapsed ALL where chemotherapy resistance has been established, particularly if there is a matched sibling donor available.

In relapsed AML, achieving rapid remission via systemic chemotherapy followed by HSCT is currently the most effective curative strategy.[59]

Immunotherapy

New immunotherapy agents continue to show promise in early clinical trials in refractory leukaemia.[88] The health service should continue to look to enrol patients in early clinical trials investigating immunotherapy agents in children and adolescents with refractory leukaemia where standard therapy has failed the patient or the patient has been unable to meet eligibility criteria.

Chimeric antigen receptor T-cell therapy

Despite significant risk of morbidity during treatment requiring high dependency or intensive care, this emerging therapy has shown promising results.[91] Chimeric antigen receptor T-cell therapy should continue to be investigated in children and adolescents with refractory leukaemia.

6.4 Supportive care in relapsed leukaemia

Treatment for relapsed leukaemia is associated with a high-risk of treatment-related morbidity and mortality, particularly infectious complications. HSCT, novel agents and cell therapies used in refractory leukaemia may also be associated with significant treatment-related side effects.

Families from regional centres may need to reside near the level five or six paediatric cancer service due to the toxicity of therapy.

Support of the patient and family, including access to information, should be managed under the family-centred care principles discussed in the 'fundamentals of care' section. Further information on relapse in children and adolescents is discussed in the 'fundamentals of care' section.

6.5 Palliative care in relapsed leukaemia

Therapies such as HSCT, treatment for high-risk AML and targeted therapies within the context of clinical trials can result in high levels of physical, psychological and existential distress, despite having curative intent. Children and adolescents with an uncertain prognosis and high symptom burden should be able to access palliative care support alongside curative-intent therapies.

Cases of relapse should trigger a referral to palliative care services, unless there are strong, family-centred reasons to decline referral. The principles of a palliative care approach need to be documented and shared with the team. The decision should be made in collaboration with the child or adolescent, and their family.

Discussion should be held within a paediatric leukaemia MDM to offer the family referral to palliative care services where there is a likely need to escalate care to manage symptoms and distress in high-risk curative regimens such as HSCT, as well as support when cure is no longer the intent of the MDT.

Scenarios that should prompt the discussion of early referral by the MDT to palliative care include:

- infant leukaemia, particularly associated with mixed-lineage leukaemia and hypodiploidy
- allogeneic HSCT, particularly in high-risk leukaemia
- AML expressing high-risk criteria
- high-risk leukaemia where induction treatment has failed the patient.

STEP 7: End-of-life care

Step 7 is concerned with maintaining the child or adolescent's quality of life and addressing their health and supportive care needs, as well as the needs of the family, at the end-of-life.

Discussion should be held within a paediatric leukaemia MDM to determine patients for whom no further disease-modifying therapy is warranted, to identify those approaching end-of-life, ensuring palliative care services are in place.

Referral to palliative care service should occur at this time, if not already engaged.

Interventions and responsibilities at the end-of-life are discussed in the 'fundamentals of care' section.

Issues at the end-of-life that are specific to children and adolescents with leukaemia include the following:

- *Blood products.* Children with advanced leukaemia often experience pancytopenia and require frequent transfusions. However, transfusion of blood products can have associated burdens, including travel time and inpatient time, as well as the risks of fluid overload and transfusion reactions. The provision of ongoing transfusions should be based on a case-by-case assessment of the child and their experience, rather than just the blood count
- *Antibiotic use.* Children with advanced leukaemia are often profoundly neutropenic and at risk of severe infection. As a child's functional status deteriorates, some families prefer to avoid the burden of prolonged inpatient admissions for infection by limiting antibiotic intervention to those able to be administered in the home, or to simply reduce the symptoms of infection. Discussing the different options for infection intervention, and the likely impact on the child, is crucial in supporting patient and family preferences.

Ongoing commitment to continuous improvement in the treatment of acute leukaemia

Due to its prevalence in childhood cancer (despite excellent overall survival), leukaemia remains one of the largest causes of cancer deaths in children.[92] Key strategies for paediatric health services to prioritise include:

- continued work in establishing the cause of childhood leukaemia
- improving risk stratification through establishing biologically-defined subgroups
- improving technologies in measuring minimal residual disease and other high-risk subgroup
- reducing the incidence of long-term toxicities from therapy
- improved development of molecularly-targeted therapies
- improved technologies in cellular therapies in treating leukaemia
- improving compliance to therapy, particularly adherence to maintenance therapy
- identifying best-evidence practices for minimising physical and psychosocial suffering and optimising quality of life for children with leukaemia in both curative and palliative treatment phases.

SECTION 3:

PAEDIATRIC ONCOLOGY CARE PATHWAY — CENTRAL NERVOUS SYSTEM (CNS) TUMOURS

This oncology care pathway outlines seven critical steps for children diagnosed with CNS tumours. While these steps are portrayed in a linear time model, in practice, patient care is rarely straightforward and predictable. The critical steps will require realignment and adjustment to best meet the needs of patients, their families and care providers without undermining the effectiveness of the treatment and supportive care program. The pathway describes the optimal cancer care that should be provided at each step.

The key principles and fundamentals of paediatric oncology practice outlined in the 'fundamentals of care' section underpin the oncology care pathway for CNS tumours.

Scope

This oncology care pathway is intended as a resource in managing children and adolescents diagnosed with CNS tumours.

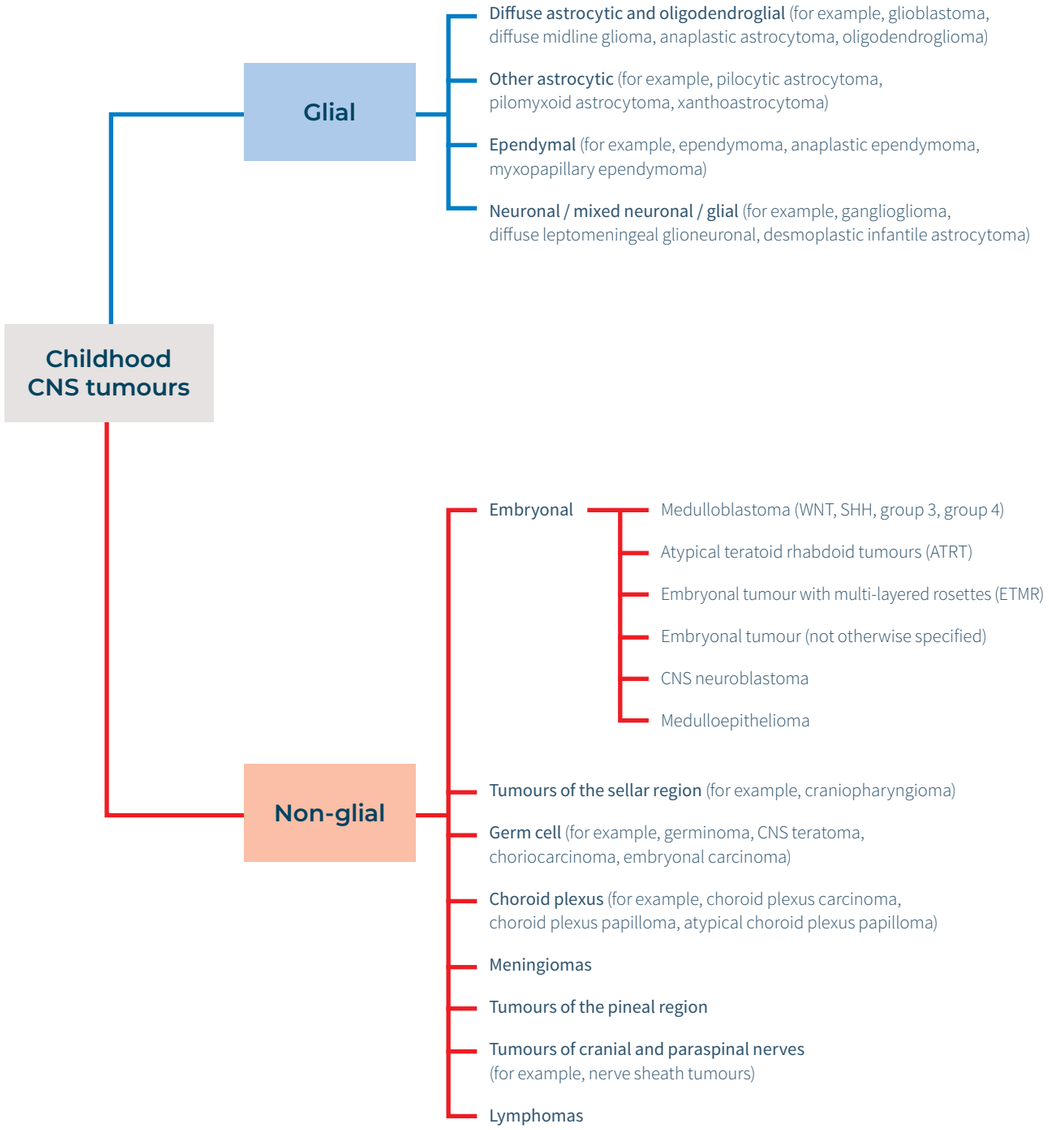
Critical time points

As mentioned at the beginning of this document the blue clock symbol is used to highlight a critical time point that has a specific timeframe attached to it.

A red clock symbol indicates the time point is part of an **urgent pathway**.

Classification of CNS tumours seen in children and adolescents [93,94]

Figure 4: CNS tumours classification, WHO 2016



Based on the understanding of the molecular and genetic basis of cancer, the World Health Organization (WHO) introduced changes in the 2016 classification of CNS tumours. The aim of these changes was to provide a combined phenotypic and genotypic diagnosis that more accurately defines real biological entities.[94] It is important for health professionals to be aware of these changes to the nomenclature to guide patient management, steer enrolment in clinical trials, provide reproducibility and support prognosis.[94]

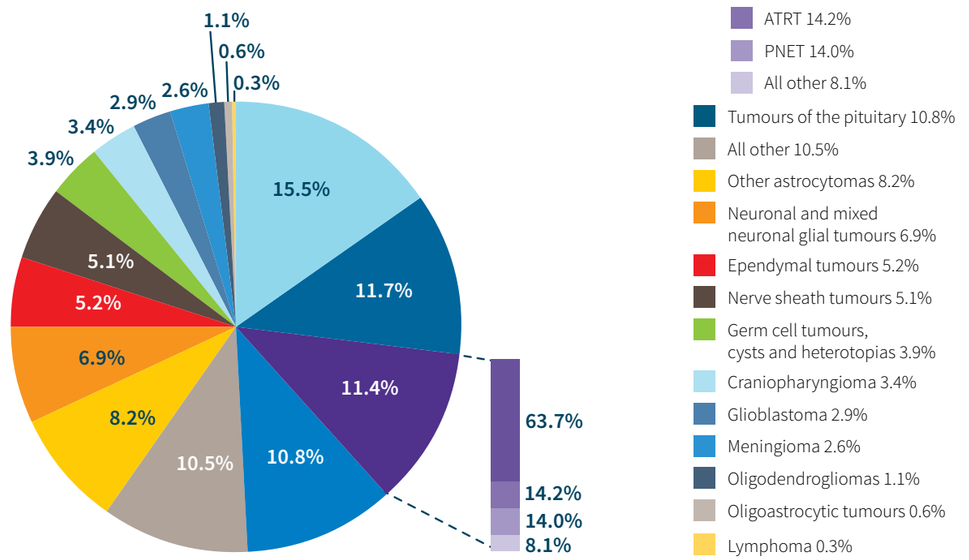
All new diagnoses of CNS tumours in children and adolescents should be classified according to the most recent WHO classification.

Many health services and government cancer registries do not keep complete data on non-malignant CNS tumours in children and adolescents. However, international data shows us that many of these children also use oncology and rehabilitative services.[95] As resource allocation is often based on population figures, it is important that health services and cancer registries work together to incorporate all CNS tumours within the cancer registry.

Distribution of CNS tumours seen in children and adolescents

CNS tumours in children and adolescents are a heterogeneous group of malignancies, creating a challenge for clinicians. Figure 5 (based on 2007 WHO data, superseded in 2016) provides an outline of the distribution of CNS tumours in children and adolescents according to histology.[96]

Figure 5: CNS tumours distribution 0–19 years, n = 16,653 (WHO 2007 histology)



Summary

Figure 6: Paediatric oncology care pathway summary — CNS tumours

Assess supportive and/or palliative care at every step of the pathway and refer to the appropriate health professional

STEP 1
Prevention and early detection

RISK FACTORS. Risk factors. There is no clear cause for most CNS tumours in children and adolescents. Some cancer predisposition syndromes may increase the risk of developing CNS tumours. Ionising radiation to the brain and spine (such as previous radiotherapy) is an established risk factor.

There are no efficient screening programs for early detection of de novo CNS tumours in the general population of children and adolescents. There is no evidence that lifestyle plays a role in the development of CNS tumours in children and adolescents.

STEP 2
Presentation, initial investigations and referral

SIGNS AND SYMPTOMS. The clinical features of CNS tumours are diverse and are dependent on the site of the tumour, the child's age, developmental level and tumour type. The possibility of a CNS tumour as a differential diagnosis should be considered in all patients with new seizures and/or focal neurological deficits. Escalation for further investigations should be considered for those patients presenting with non-localising symptoms that fail to settle or progress rapidly.

Non-localising signs and symptoms may include nausea, vomiting, headaches, drowsiness, lethargy, irritability, confusion, growth and endocrine disorders, altered gait, poor coordination, rapid visual changes, behavioural changes and increased head circumference. Primary care and emergency departments should have access to current evidence-based information to guide investigation and referral in the suspicion of a CNS tumour in a child or adolescent.

PARENTAL CONCERN. Escalation for further investigations is also warranted if there have been repeated GP visits or a high level of parental anxiety.

REFERRAL. Paediatric tertiary referral centres should provide clear routes of rapid access for GPs and community paediatricians to specialist evaluation.

STEP 3
Diagnostic work-up, staging and treatment planning

DIAGNOSIS. MRI with contrast of the entire craniospinal axis is the preferred imaging technique for diagnosis. All imaging results should be interpreted by a radiologist with experience in CNS imaging in children. In most cases, a definitive diagnosis will be made via examination of a tissue sample. Access to molecular profiling of tumour samples should also be used when available.

TREATMENT PLANNING. Optimal treatment planning includes presentation of all patients with CNS tumours at a state-wide paediatric neuro-oncology MDM.

STAGING. Level five and six paediatric cancer services should use standardised grading systems tailored to specific CNS tumours and, when available, these tumours should also be risk-stratified according to molecular profiling.

COMMUNICATION. The lead clinician should discuss the outcomes of the MDM with the patient and family, including the diagnosis, risk assignment, treatment plan and, where appropriate, access to clinical trials. The plan should be communicated with the original referring clinician, the GP and paediatrician if applicable.

STEP 4
Treatment

TREATMENT. Treatment protocols must aim to offer the best curative approach while reducing morbidity.

Neurosurgical interventions should be organised within a state-wide paediatric neuro-oncology MDT structure.

CLINICAL TRIALS. When available, clinical trials should be offered to all children and adolescents with CNS tumours. For patients who do not meet trial eligibility criteria, the most recent, evidence-based and published study protocol offering the best outcomes should be used.

Chemotherapy is often prescribed within validated treatment protocols.

Targeted therapies are also increasingly being utilised in CNS tumours. Consideration of **Radiotherapy**, often a key component of treatment, will be discussed within the state-wide paediatric neuro-oncology MDM. **Rehabilitative** care packages with multidisciplinary support should be available to patients diagnosed with CNS tumours.

COMMUNICATION. The lead clinician should discuss the treatment protocol, including intent, risks, benefits and supportive care measures, with the patient and family. The care plan should be communicated with the GP and paediatrician if applicable.

Assess supportive and/or palliative care at every step of the pathway and refer to the appropriate health professional

STEP 5
Care after completing therapy and survivorship

COMING OFF TREATMENT. All patients should have an end-of-treatment consultation with their primary oncologist and, if applicable, their neurosurgeon and clinical trials coordinator, and be provided with a surveillance roadmap.

SURVIVORSHIP. All patients completing treatment for CNS tumours will be referred to a survivorship program within three months to formulate a shared care plan between the acute and survivorship services. Minimum documentation should include a treatment summary and a tailored survivorship roadmap for future tests and investigations.

TRANSITION OF CARE. In most cases, transition of adult survivors of a childhood CNS tumour should be to their GP. Transition of patients with actual or a high-risk of possible late effects that require speciality care should be referred to adult speciality facilities. All CNS tumour survivors with ventriculoperitoneal (VP) shunts in situ should have annual reviews by an adult neurosurgeon beyond transition.

STEP 6
Managing refractory disease or relapse

DETECTION. Most instances of relapse or recurrence are identified through routine clinical examination or medical imaging.

TREATMENT PLANNING. Optimal treatment planning requires presentation to a state-wide paediatric neuro-oncology MDM . Early integration to palliative care services (and advance care planning) should also be considered.

TREATMENT. Children may be eligible for enrolment in clinical trials. Treatment may involve further surgery, radiotherapy or chemotherapy.

COMMUNICATION. The lead clinician should discuss the outcomes of the state-wide paediatric neuro-oncology MDM with the patient and family, including treatment options, the nature and intent of any treatment, potential clinical trial enrolment, prognosis and risks and benefits of treatment. The plan should be communicated with the GP and/or paediatrician.

Assess supportive and/or palliative care

STEP 7
End-of-life care

PLANNING. An advance care plan specific to end-of-life care should be documented early in this stage. Elements of end-of-life care should be guided by evidence and/or expert consensus.

COMMUNICATION. The advance care plan should be communicated in the patient file and shared with the GP and/or paediatrician.

Step 1: Prevention and early detection

This step outlines recommendations for the prevention and early detection of CNS tumours.

1.1 Prevention

Although risk factors have been identified, there is no clear cause for most CNS tumours. There are no proven or recommended preventative strategies. There is no evidence that lifestyle plays a role in the development of CNS tumours in children and adolescents. It is important to ensure the patient and their family are aware of this to avoid feeling responsible for the diagnosis.

1.2 Risk factors

Genetic predisposition and host factors

Some cancer predisposition syndromes can increase the risk of developing a CNS tumour in childhood.[97] These include, but are not limited to, neurofibromatosis types 1 and 2, tuberous sclerosis, Li-Fraumeni syndrome and hereditary retinoblastoma.[98] When treated for cancer, some patients who carry genetic predisposition may also have an increased risk of secondary cancers within the field of radiation of the primary tumour.[99] See the 'fundamentals of care' section for more information regarding genetic predisposition.

Environmental factors

Moderate to high-dose ionising radiation is an established risk factor for developing CNS tumours.[100] In nearly all cases, this is a result of radiotherapy administered to treat cancer.[101] There has also been previous history of CNS tumours from craniospinal radiotherapy in the treatment of childhood leukaemia.[99] Currently, there are no other identifiable environmental factors (including mobile phone technology and powerlines) that have a significant association with the development of childhood CNS tumours.

1.3 Screening and early detection

Children and adolescents with a high predisposition to develop CNS tumours should have medical consultations, according to the most recent published guidance, with a medical expert specialising in these conditions. For the general population without an underlying predisposition, there is no efficient screening program for detecting de novo CNS tumours.

Step 2: Presentation, initial investigations and referral

Tumours of the CNS in children and adolescents are rare. This represents a major diagnostic challenge for emergency departments and GPs.

This step outlines the process for establishing a provisional diagnosis and appropriate referral for a child or adolescent suspected of having a CNS tumour.

2.1 Presenting signs and symptoms

The clinical features of CNS tumours are diverse, often non-specific and dependent on the site of the tumour, the child's age, developmental level and tumour type. There is no single clinical finding that is characteristic for all CNS tumours in children and adolescents,[99] and the predictive power of isolated non-localising signs and symptoms is weak.[102] Furthermore, signs and symptoms are often subtle and mimic more common childhood conditions.[103] Despite this, health professionals in primary practice and emergency settings should develop an awareness of CNS tumours in children and adolescents in order to make appropriate and timely referrals.[58]

Delays in diagnosis may be associated with inferior outcomes and/or increased morbidity. Although tumour biology and treatment response are the strongest indicators of outcome, when considered across all CNS tumour types, children who experience a long diagnostic time interval are more likely to present with significant neurological deficits at diagnosis,[104] resulting in greater long-term complications such as visual loss and endocrinopathies.[104,105] A delay in diagnosis can also have major psychological impacts on patients and their families, and their subsequent health-seeking behaviour.

Although non-localising signs and symptoms in isolation do not have high predictive power for diagnosis, their rising frequency and severity is consistent in all CNS tumours,[102] and should influence a decision to seek further investigations. It is important to also recognise parental concern; escalation for investigations should be warranted after repeated visits or high levels of parental anxiety.[60]

The possibility of a CNS tumour as a differential diagnosis should be considered in all patients who present with new seizures or focal neurological deficits.

For patients who present with non-localising signs and symptoms that fail to settle, or progress rapidly, further investigations should be considered, rather than relying on the presence or absence of specific signs or symptoms.[102]

Non-localising signs and symptoms may include, but are not limited to, nausea, vomiting, headaches, papilloedema, drowsiness, lethargy, irritability, confusion, growth and endocrine disorders, declining school performance, altered gait, poor coordination, rapid visual change, behavioural changes and increased head circumference. Presence of two or more symptoms should escalate concern.

Work has been undertaken in the United Kingdom (UK) and North America in raising awareness of early clinical features of CNS tumours in children and adolescents.[106,107] This pathway supports initiatives aimed at increasing this understanding. A framework such as the UK HeadSmart[108,109] guidance for health professionals and consumers should be adapted and implemented. Level five and six paediatric cancer services should adopt and actively promote such information and educational resources among the primary healthcare network, local emergency departments and general paediatricians.

Primary care and emergency departments should have access to current evidence-based information to guide investigation and referral in the suspicion of a CNS tumour in a child or adolescent. This guidance should be adapted for local needs and promoted by the level five or six paediatric cancer service.

Paediatric cancer services should monitor key indicators such as time to diagnosis and aim to achieve time intervals that are at least comparable or better than best practice international published data.

2.2 Referral

The following recommendations encourage the use of a decision-support tool such as the UK HeadSmart initiative[109] for supporting (or eliminating) the diagnosis of a CNS tumour in children and adolescents.

- All children and adolescents seen in primary or emergency care with a high suspicion of a possible CNS tumour should be discussed on the same day with a paediatric tertiary health professional. A high suspicion may include new seizures, focal neurological signs or non-localising signs that have increased in frequency and intensity.
- The paediatric tertiary referral centre should be able to offer rapid, same-day access for telephone consultation for primary and secondary care health professionals managing a child with a high suspicion of a CNS tumour.

The GP or paediatrician should have a clear process for rapid paediatric tertiary referral and transfer, in both emergency and outpatient based-presentations.

The minimum documentation for referral should include:

- a referral letter, including the patient's demographics, relevant medical history, medications and allergies
- results of any clinical investigations (including imaging and pathology reports)
- the need for interpreter services and other recognised significant psychosocial issues.

The GP or paediatrician should aim to provide electronic or printed confirmation of tests and investigations, but availability should not delay the referral.

2.3 Initial investigations

Medical imaging is the primary modality for the initial diagnosis of CNS tumours.[99] Health services should be able to demonstrate rapid access to medical imaging, including services that can deliver sedation or general anaesthesia to infants and young children. If general anaesthesia services for medical imaging cannot be delivered in a timely manner, the patient must be referred to a centre with this capability. MRI of the entire craniospinal axis is the preferred modality for all children and adolescents with a suspected CNS tumour.[104] The preference of MRI over CT scanning in children and adolescents with CNS tumours includes the ability to provide superior resolution of the images with

improved anatomical detail without exposure to ionising radiation.[99] The use of CT scans should be minimised in situations outside of the emergency setting and, if used, should utilise contrast enhancement. All imaging results should be reported by a radiologist with experience in CNS MRI and CT scans in children,[108] and be available to report results in real time for urgent imaging.

MRI should be the imaging technique of choice in all children and adolescents with existing or suspected CNS tumours.

Health services should be able to provide prompt access to MRI, including imaging under general anaesthesia.

CT scanning may be necessary in emergency situations because it can be performed rapidly without the need for general anaesthesia.

All urgent imaging should be reported in real time by a radiologist experienced in paediatric imaging.

- All children with a high suspicion of a CNS tumour should have arrangements made for urgent CNS imaging (preferably MRI) within 24 hours.
- Telephone consultation with a level five or six paediatric cancer service should be encouraged when planning imaging to exclude the differential diagnosis of a CNS tumour (a low suspicion of a CNS tumour). Imaging required to exclude a differential diagnosis should be performed as soon as practical (optimally within two weeks). Consideration of other differential diagnoses should not cease.

Step 3: Diagnostic work-up, staging and treatment planning

Step 3 outlines the process for confirming the diagnosis and planning subsequent treatment. The guiding principle is that interaction between appropriate multidisciplinary team members should be responsible for determining the treatment plan. The definitive diagnosis of a CNS tumour nearly always requires surgical biopsy.

It is a requirement that diagnostic work-up, staging and treatment planning of children and adolescents with CNS tumours should be undertaken within a level five or six paediatric cancer service.

3.1 Diagnostic work-up and pre-treatment investigations

Physical examination, assessment and history

A physical examination and assessment should be undertaken and documented as a baseline on presentation to a level five or six paediatric cancer service. This should incorporate a comprehensive, developmentally appropriate neurological examination. A baseline examination provides for ongoing comparison during treatment and surveillance. Head circumference, particularly in children under four years, should be documented on growth charts and when available, compared with previous measurements. A normal examination does not exclude a CNS tumour in children and adolescents[109] and other modalities are still necessary to aid diagnosis.

A history of comorbidities and all symptoms elicited from the patient and caregiver (including time of onset, frequency and severity) should be obtained. A history of any regression or failure to achieve developmental milestones, academic performance (particularly declining performance), behavioural changes, growth failure and delayed or arrested puberty should also be recorded.

When diagnosis is confirmed, a comprehensive family cancer history extending back three generations can help further identify patients and families with inherited cancer predisposition syndromes.[54]

- A detailed history, physical and age-appropriate neurological examination should be undertaken and documented on the day of presentation to the level five or six paediatric cancer service for all children and adolescents with a suspicion of a CNS tumour.

Medical imaging interventions

As previously discussed, medical imaging is the primary modality for the initial diagnosis of CNS tumours.[99] MRI with contrast of the entire craniospinal axis is the preferred imaging technique prior to surgery. If a CT scan is undertaken as part of the initial workup, an MRI should be performed prior to any definitive diagnosis and treatment planning.

Surgical interventions at diagnosis

In nearly all cases, a definitive diagnosis will require examination of a tissue sample following biopsy or resection.[110] The indications and considerations for surgical intervention are further discussed in Step 4. Surgery is also indicated upfront in urgent cases, such as obstructive hydrocephalus, haemorrhage or significant mass effect.

The level five or six paediatric cancer service should be able to demonstrate urgent pathways for emergency management of CNS tumours, including after-hours services. This should incorporate neurosurgery, oncology, medical imaging, anaesthetics, intensive care, radiation oncology, pathology (including biobanking and discussion of clinical trial samples) and other medical specialties as needed.

Diagnostic laboratory investigations

As well as performing tissue biopsy, for many presentations additional diagnostic interventions may need to be undertaken according to the pathology of the tumour and risk of metastatic disease. Understanding the full extent of disease at diagnosis is vital for optimal treatment planning and prognosis.[111]

3.2 Grading, risk stratification and biobanking of CNS tumours

CNS tumours rarely metastasise to organs outside of the craniospinal axis, but they commonly spread within the CNS. Staging, therefore, if used, is generally limited to CNS metastases. Grading of a tumour, from differentiated (low-grade) through to undifferentiated (high-grade) is frequently used, such as grading of gliomas. Stratifying risk according to variables such as age, presence of metastases and residual tumour following resection are applied to CNS tumours.[112] Due to the heterogeneity of CNS tumours, no one system for risk assessment can be applied, as the criteria for identifying risk are often tumour-specific. Increasingly, molecular analysis of CNS tumours will play a role.

Molecular profiling of CNS tumours in children and adolescents

Incorporating genomics into the treatment of CNS tumours is progressing at a rapid rate.[113] Health professionals managing children and adolescents with CNS tumours require an understanding of precision medicine in which the diagnosis, classification and treatment of paediatric CNS tumours are informed by their molecular and genomic characteristics.[114] Advances in molecular dissection and analysis of CNS tumours and their subgroups will alter future clinical care by significantly improving the accuracy of diagnosis, prognostication and identification of appropriate therapies.[113,115] Rapid transition of these new technologies to the clinical setting will demand continued efforts and collaboration across national and multinational groups.[113]

Biobanking

To support the application of precision medicine in patients with CNS tumours (where subgroups of rare cancers are increasingly identified and thereby less common), access to biobanks with high-quality, well-described neuro-oncology bio-specimens is critical.[116]

The level five or six paediatric cancer service should use standardised systems for grading and/or staging CNS tumours and, when available, these tumours should also be risk-stratified according to molecular profiling.

Molecular classifications and CNS nomenclature identified by the health service should be consistent across international study groups to encourage rapid translation of findings for these small and rare patient cohorts.

The level five and six paediatric cancer services should develop sustainable ethical and clinical governance structures for the biobanking of CNS tumours in children and adolescents that also collaborate with external institutions to encourage rapid translational research.

3.3 The multidisciplinary team and treatment planning

Collaborative, multidisciplinary discussion is recognised as an essential tool for managing paediatric cancer.[117] Surveys of European practices show that they are utilised in nearly all paediatric oncology services.[117] In adult cancer, MDMs have been shown to lead to significant changes in the way cancer patients are assessed and managed.[118] The MDM is considered a central part of the cancer pathway and a gold-standard of cancer care globally.[119] All paediatric cancers are rare by nature and therefore children benefit from treatment plans discussed and agreed upon in MDMs. Hence, the whole paediatric oncology community may benefit from the introduction of a well-established, state-wide paediatric neuro-oncology MDM that is convened to share knowledge and expertise.

The neuro-oncology multidisciplinary team

Optimal treatment planning includes presentation of all patients with CNS tumours at a state-wide paediatric neuro-oncology MDM.

It is a requirement that the state-wide paediatric neuro-oncology MDM include all the experts required for the diagnosis and treatment planning of childhood CNS tumours including:

- paediatric oncologist with a subspecialty in neuro-oncology*
- pathologist with experience and expertise in paediatric CNS malignancies*
- nurse consultant with experience and expertise in paediatric CNS malignancies*
- neurosurgeon with experience and expertise in paediatric CNS malignancies*
- radiologist with experience and expertise in paediatric CNS malignancies*
- radiation oncologist with a subspeciality in paediatrics*
- paediatric clinical trials coordinator
- paediatric oncology pharmacist
- social worker with experience in paediatric oncology
- paediatric palliative care clinician
- neuropsychologist.

*Core members of the MDT who will be represented in person or remotely at the time of the meeting.

Ideally, all core members within the institution will attend the state-wide paediatric neuro-oncology MDM, regardless of whether they have patients to present. A secondary but important outcome of the state-wide paediatric neuro-oncology MDM are the educational opportunities they provide for all participants.

Administrative support should be available to ensure efficient documentation and dissemination of meeting recommendations and regular audits to monitor the quality of the meetings.

A referral is made to the oncology team within 24 hours of presentation for all new diagnoses.

Discussion at the state-wide paediatric neuro-oncology MDM should occur within two weeks of presentation to the level five or six service and be clearly documented in the patient record in real time.

Communication of the state-wide paediatric neuro-oncology MDM recommendations

The lead clinician should discuss the outcomes of the state-wide paediatric neuro-oncology MDM with the patient and family, including the diagnosis, risk assignment, treatment plan and, if appropriate, access to clinical trials. The plan should be communicated with the original referring clinician, the GP and, if applicable, the child's paediatrician. Where possible, further planning discussions with the family should be collaborative and multidisciplinary and incorporate oncology, neurosurgery and radiotherapy, as applicable.

Consultation with external services

CNS tumours in children and adolescents are rare and may benefit from other centralised paediatric cancer services for further opinion. Level five or six paediatric cancer services should be able to demonstrate effective and timely links to and relationships with paediatric cancer services nationally, as well as other international centres of excellence, when further opinion is required. This type of effective collaboration when diagnosing and treating rare cancers should be encouraged by the health service and clearly communicated to the families. It is acknowledged that a definitive diagnosis in some rare cancers may be delayed due to the need to collaborate with other centres.

Reporting the diagnosis

All new diagnoses are reported to the state cancer registry. Any changes in a child's final diagnosis will be updated in the state cancer registry.

3.4 Supportive care considerations

Supportive care considerations applicable to all children and adolescents with cancer are discussed in the 'fundamentals of care' section. Additional supportive care requirements in the context of children and adolescents with CNS tumours at diagnosis are discussed below. Rehabilitation in the context of CNS tumours is addressed in Step 4. It is important to acknowledge the supportive care needs of children with either malignant or benign/low-grade CNS tumours.

All children and adolescents with CNS tumours should have an ongoing, universal referral made to social work at the time of diagnosis.

Endocrinology

Children and adolescents with CNS tumours, particularly those that involve the hypothalamus or pituitary gland, may present with endocrinopathies prior to diagnosis.[120] These may develop acutely after therapy. Survivors of childhood CNS tumours are at a significant increased risk of endocrine late effects, with studies showing an incidence of up to 40 per cent.[121] Diagnosing and treating both early and late presentations in a timely manner will improve growth, wellbeing and quality of life.

All patients with CNS tumours who have a proven, or are at risk of, endocrinopathy should be referred to a paediatric endocrinologist who has experience working with children and adolescents with cancer. If clinically required, the paediatric endocrinologist should remain part of the MDT for consultation throughout surveillance and survivorship.

Neuropsychology

Children and adolescents with CNS tumours have a markedly higher risk of neurocognitive impairment compared to their healthy peers.[122] Younger patients and those receiving cranial radiotherapy have the highest risk for such impairment.[111]

Neuropsychological care for patients with CNS tumours should be managed in line with risk algorithms defined within the PICS document *A compendium of evidence and framework for neuropsychological services in paediatric cancer (2015).*[34] Screening should be completed with standardised measures[23] by a psychologist with experience in CNS tumours in children and adolescents.[123]

3.5 Communication with the patient and family

Lack of access to information has been identified as a cause of stress and conflict for families of children with cancer.[71] The family and patient will be provided with both verbal and written information, as appropriate to the family's health literacy, that should include the following topics:[72]

- diagnosis, treatment plan, treatment intent and prognosis
- management of fever and neutropenia (if applicable)
- side effects of treatment
- who/how to call their hospital and/or treating team
- access to clinical trials
- managing medications and compliance at home
- central line care (if applicable)
- caring for the child at home
- supportive care
- orientation to the hospital and overview of the healthcare team (key members)
- preventing infection
- blood counts
- follow-up appointments
- fertility optimisation options (if applicable)
- psychosocial issues.

Information for families of children with CNS tumours may include:[72]

- raised intracranial pressure/hydrocephalus
- seizures
- shunt malfunctions (if applicable)
- vomiting
- steroid side effects
- post-operative wound care
- headaches
- radiotherapy (if applicable)
- physical limitations
- rehabilitation
- cognitive limitations
- bleeding precautions
- nutrition.

Both verbal and written family education information should be provided following diagnosis and include information targeted to children and adolescents.

Consideration must be made and strategies put in place for communicating with families with cultural and linguistic diversity, including providing access to interpreter services and translated educational materials.

Age and developmentally appropriate information should be available for children and adolescents.

Advice at home

The paediatric cancer service should provide a standardised service allowing timely and consistent remote support monitoring via the telephone for patients and their families when at home.

Step 4: Treatment

Step 4 outlines a framework for delivering treatment for CNS tumours in children and adolescents.

Effective strategies to improve overall survival and reduce late effects are identified through international collaborative clinical trials.

4.1 Treatment intent

For most children and adolescents with CNS tumours, the goal of care and treatment intent at diagnosis is cure, or control of disease with preservation of function. Currently, for some patients with certain tumour types there is no effective treatment. Similarly, for patients who experience a recurrence of the CNS tumour, effective treatment options are often limited. Management strategies for patients with such tumour types and those who develop refractory or relapsed disease are discussed in Step 6.

4.2 The role of clinical trials and research in CNS tumours

The landscape in the management of CNS tumour biology and treatment is undergoing a rapid transition as new molecular pathways and genetic changes are discovered.[124] Clinical trials will require comprehensive molecular classification of these new pathways at diagnosis and, given the rarity of subsequent subgroups, trials will need to be multi-institutional and international.[125] Advances can be accelerated by making well-annotated biological samples linked to patient outcome data available to researchers.[126]

The level five and six paediatric cancer services will encourage the development of and/or participation in multi-institutional collaborative clinical trials for childhood CNS tumours.

Clinical trial enrolment should be offered to all patients where open trials are available. For those who do not meet eligibility criteria, or where a clinical trial is not open, the patient should be treated according to the most recent, evidence-based and completed study protocol.

The level five and six paediatric cancer services should be able to demonstrate effective collaboration with other centres of excellence to meet standards for trials enrolment and access to novel agents.

4.3 Surgery

Neurosurgery is the initial step of the treatment pathway for most patients with CNS tumours. For many patients, gross total resection of the tumour (when it is safe to do so) correlates with improved survival rates.[111] However, there are real risks that significant permanent neurological impairment may result from excessive focus on this goal. Therefore, a carefully balanced approach is required to achieve the goal of maximising the extent of resection while minimising the risk of permanent neurological or neuropsychological sequelae.

Outcomes have also been shown to improve with the centralisation of neurosurgical procedures,[127] with the evidence supporting lower mortality/morbidity rates of CNS tumour patients in high-volume, specialised hospitals.[128,129] The volume of patients seen will also improve institutional experience and memory[130] in areas such as the intensive care setting, as well as active participation by neurosurgeons in a state-wide paediatric neuro-oncology MDM. The high-volume effect and outcomes in paediatric neuro-oncology has not been demonstrated in all studies.[131] Institutional volume of patients should be considered alongside services that encourage and support speciality paediatric neuro-oncology teams under a state-wide MDM structure. In such settings, the volume of individual surgeons is also an important consideration for providing an effective service.[132,133]

Neurosurgical interventions for treating CNS tumours should be organised within a paediatric neuro-oncology MDT structure with a limited number of neurosurgeons (with experience and training in paediatric neurosurgery) to ensure volume effect.

Indications

Indications for surgery, including both the need for biopsy and/or resection and emergency interventions, vary considerably according to tumour type and location. The treatment for many tumour types (as well as the rapid understanding of their molecular characteristics) has evolved over time and will likely continue to evolve, meaning neurosurgical interventions for individual patients are best organised within a neuro-oncology MDT structure.[99] When surgery is recommended, it should be taken under the consideration that all interventions aim to preserve brain function while maximising tumour resection and minimising morbidity.[134]

Recommended timings

- For patients with CNS tumours who present with an altered level of consciousness from mass effect, surgical interventions (based on neurosurgical assessment) should be performed urgently (on the same day). Optimally, this will occur within a paediatric neurosurgical setting.
- For patients with CNS tumours who are alert but have a demonstrable mass effect on assessment and imaging, surgery should optimally be performed within 24 hours in a paediatric neurosurgical setting.
- For patients with smaller lesions without risk of mass effect, therapy should be guided by the state-wide paediatric neuro-oncology MDM, diagnostic and clinical trial requirements, as well as the level of institutional resources available to provide optimal care.

Communication

- Discussions should occur between the neurosurgical and oncology teams prior to any planned neurosurgery.
- Optimally, all planned neurosurgery should be first discussed at a state-wide paediatric neuro-oncology MDM, where timing allows. This is of greater importance in complex cases or where the surgical technique is not well delineated.
- All neurosurgical procedures for oncology patients should be presented at the state-wide paediatric neuro-oncology MDM within two weeks of surgery.

Anaesthesia

Children with CNS tumours pose added risks when providing general anaesthesia. Such patients may have impaired function (metabolic and physical) such as electrolyte disturbances, dehydration, seizures, cranial nerve palsies and hypothalamic/pituitary hormonal deficiencies, and require experienced paediatric anaesthetic services.[135] Dedicated anaesthetic support is provided across the pre-and post-operative period, including intensive care. For all planned interventions (and ideally in the emergency situation) the anaesthetist should be able to demonstrate training, clinical expertise and professional development in delivering anaesthesia in paediatric neurosurgery and have regular work responsibilities in this field.[136]

Theatre environment and technologies

All planned neurosurgery should be undertaken in an appropriately equipped operating theatre. In addition to a specialised medical and nursing workforce, intraoperative technologies and techniques for consideration include spinal cord monitoring, neuro-endoscopy, EEG monitoring, cavitating ultrasonic aspirator, evoked potential testing, operating microscope and neuronavigational techniques.[136,137]

In older children and adolescents, the use of intraoperative neurophysiological mapping under local anaesthesia and sedation can provide real-time feedback during surgery to avoid damage to eloquent brain structures.[49,137,138] Consideration should be undertaken when clinically relevant.[134]

Post-operative care

Health services will be able to demonstrate access to paediatric intensive care services and inpatient step-down wards (with appropriately trained and experienced staff) during the post-operative period. All patients should be cared for post-operatively by nurses experienced in neurology and neurosurgery.

All paediatric neurosurgical interventions will be carried out within a theatre appropriately equipped (with technologies and workforce) for neurosurgery.

Health services should continually examine novel perioperative approaches and technologies in neurosurgery that augment field of vision, maximise tumour resection and reduce morbidity, under the auspices of ethical and clinical governance and a MDM structure.

For non-urgent cases, the decision to utilise different approaches (which may determine the place of care) should be made at the state-wide paediatric neuro-oncology MDM prior to surgery, when clinically appropriate.

Access to paediatric ICU services and inpatient step-down wards (staffed by health professionals experienced in paediatric neurosurgery) should be available for all planned surgical cases.

Peri-operative nursing care should be provided by staff competent and experienced in the care of paediatric neurosurgical patients.

4.4 Radiotherapy

Considerations

Radiotherapy is an essential pillar of curative and palliative treatment for CNS tumours in children and adolescents,[99] and with more conformal methods of delivery, image guidance and technologies that spare healthy tissue while offering precise targeting, at this point in time it will continue to remain so.[5] With greater numbers of survivors following treatment for CNS tumours, the long-term side effects of radiotherapy have become an important concern, and the reduction of radiation fields and dosage, where possible, is a study aim in many current clinical trials.[139]

Service capability framework for paediatric radiotherapy

Due to small numbers, patients receiving radiotherapy are treated outside the level 5 or 6 paediatric cancer services in specialist radiotherapy centres. It is important that these patients are managed under the guidance outlined in the *Service capability framework: a guide for Victorian health services providing radiation therapy to children and adolescents with cancer*, which describes the minimum service requirements for providing a coordinated, sustainable and consistent model of care for delivering radiotherapy to children and adolescents with cancer.[5]

Where available, radiotherapy should be undertaken within the context of a clinical trial and, where eligible, enrolment should be offered as standard of practice.

Radiotherapy delivered outside the context of clinical trials should be informed by evidence-based guidelines.

The pathway for delivering radiotherapy to children and adolescents with CNS tumours should follow the guidance outlined in the *Service capability framework: a guide for Victorian health services providing radiation therapy to children and adolescents with cancer.*

All patients with a history of receiving CNS radiotherapy should be formally reviewed within a survivorship service that is tailored for neuro-oncology. Data should be collected in survivorship of the treatments offered and emerging early and late effects.

Communication and collaboration

- Access to radiotherapy should be delivered as prescribed within the treatment protocol and/or clinical trial. Delays to treatment should be recorded and the reasons clarified and investigated.

All prospective treatment planning of patients requiring CNS-directed radiotherapy will be undertaken within the context of the state-wide paediatric neuro-oncology MDM and documented in the patient's medical record. A detailed referral will be sent to the radiotherapy service.

Written consent (and if applicable assent) should be sought for all patients prior to undergoing radiotherapy and documented in the patient file.

All patients, and their families, should be provided with a tailored education program regarding radiotherapy, indications, side effects and self-care, prior to any interventions.

- At the completion of the treatment, the radiotherapy service should provide a written summary for the referring level five or six paediatric cancer service that documents all radiation fields, total radiation dose to each field and the age of the first dose of radiotherapy.

Proton therapy

Proton therapy is a treatment option for CNS tumours in children with equivalent efficacy to traditional photon therapy and reduced risk of secondary cancer in some diagnoses[140] while potentially reducing dosage to healthy tissue and organs.[139] Proton therapy has also been shown to be more cost-effective for some paediatric CNS tumours.[141] However, high-quality research continues to be sought to measure efficacy in the long term.[142,143] Currently no superiority has yet been shown in the clinical data by proton therapy over advanced photon therapy in late effects of treatment.[140] At this point in time, access to proton therapy may be considered in patients with defined CNS tumour subgroups and discussed at the state-wide paediatric neuro-oncology MDM (especially when under the auspices of a clinical trial) but should not delay critical time to treatment in place of current advanced photon therapy techniques with comparable efficacy.

4.5 Chemotherapy

Indications for chemotherapy

There is a defined role for chemotherapy in treating many childhood CNS tumours. It is used as an adjunct to radiotherapy and/or surgery, as a means of reducing the morbidity associated with radiotherapy and where surgical resection is difficult.[144]

Targeted therapy

The current landscape of molecularly-classified CNS tumours provides for more personalised medicine. Investigating the success of potential novel targets should be undertaken within the context of multi-institutional, collaborative paediatric clinical trials after consideration at a state-wide paediatric neuro-oncology MDM.[145,146]

Role of stem-cell supported chemotherapy in CNS tumours

High-dose chemotherapy with autologous stem-cell return may be used in younger children with CNS tumours to avoid or delay the use of radiotherapy.

Administering chemotherapy.

- A central venous access device should be placed prior to receiving intravenous chemotherapy. This is most important in young patients, the delivery of vesicant chemotherapy protocols and those requiring myelosuppressive or stem-cell supported regimens.

- Planning and decision making for all patients receiving chemotherapy (including potential targets based on tumour characteristics) should be undertaken and documented within the state-wide paediatric neuro-oncology MDM.

Chemotherapy should be prescribed with the use of validated protocols within an electronic prescribing system.

A documented procedure that is strictly followed for the prescribing, dispensing, administering and documenting of all chemotherapy must be used within the health service.

Printed materials for families of all chemotherapy agents prescribed should be available.

4.6 Rehabilitation

Despite an increase in survivorship, morbidity from CNS tumours in children remains high.[147] Some patients will need targeted, complex rehabilitation over long periods of time to manage the neurological sequelae of both the tumour and its treatment. Although research and outcomes from neuro-rehabilitation is limited within the paediatric oncology context,[147,148] long-term outcomes in large survivorship studies show a high level of morbidity is experienced in this population, and warrants early intervention.[149,150]

Specialist care: neuro-rehabilitation care packages

In line with models of care such as that recommended by the UK National Institute for Health and Care Excellence,[9] a neuro-rehabilitation care package of support takes into account the impact of disease and treatment of neurological, physical, psychological and academic function.[9] The MDT should include (but not be limited to):

- speech and language therapy
- physiotherapy
- occupational therapy
- neurology
- clinical and neuro-psychology
- rehabilitative nursing
- teacher/school liaison
- rehabilitative medicine
- social work.

Level five and six paediatric cancer services should ensure that multidisciplinary care packages of support are provided to patients diagnosed with a CNS tumour who require neuro-rehabilitation.

When applicable, referral to a neuro-rehabilitative team should be made via the neuro-oncology MDT and occur at the time of diagnosis. Interventions should occur concurrently with treatment and not be delayed until the child enters surveillance or survivorship.

An interventional program of neuro-rehabilitation should continue as a long as there is a demonstrable effect.

4.7 Place of care

Treatment for CNS tumours is managed at a level five or six paediatric cancer service, in line with the *Service capability framework: a guide for Victorian health services providing primary treatment and shared care to children and adolescents with cancer.*[4] Consideration for supportive care and some aspects of treatment such as administering low-complexity chemotherapy in paediatric centres closer to the child's home should be made within the neuro-oncology MDT. Shared care centres are required to adhere to the standards outlined in the framework. Episodes of chemotherapy in regional shared care centres should be conducted with the use of telehealth between the local health service and the patient's oncologist.

For regional families, a discussion within the MDT should occur and be documented for potential shared care opportunities within the local scope of practice, including chemotherapy, rehabilitation, supportive care and ongoing imaging (with the use of image sharing software). Regional care should be delivered under the supervision of a consultant paediatrician, who has established links to the level five or six paediatric cancer service via telehealth and access to electronic communication.

For metropolitan families, efforts should be made to support localised and home-based care, when it is safe to do so.

4.8 Adherence and compliance to treatment for CNS tumours

Caring for a child or adolescent with a CNS tumour can be very challenging for the healthcare team and the child's family. These patients require multidisciplinary input to manage their disease, side effects of treatment and ongoing comorbidities. Some treatments are prolonged and involve more than one oral chemotherapy agent to be administered in the home. As well as anti-cancer therapy, many of these patients require other regular medications in the home, which may be prescribed from different healthcare teams. These include medicines for supportive care, antiepileptic drugs and hormone replacement therapy, which can have immediate adverse health effects when not administered correctly. Enrolment on clinical trials for novel targeted therapies also requires strict documentation and monitoring for study compliance. Finally, it is also important to maintain compliance with regular timed appointments for physical examination and medical imaging.

The level five or six paediatric cancer service should have in place a mechanism to measure and record compliance with home-based oral medication administration, including how changes to oral chemotherapy and other medicines are communicated to families in both written and verbal forms.

Health services should be able to deliver strategies to ensure families of patients with chronic and complex needs are able to meet the demands of treatment and supportive care. This is particularly applicable to those patients enrolled on early phase trials, families with cultural and linguistic diversity, regional and remote families, those with low socioeconomic status and those with low-level health literacy.

Health services should be able to provide telephone access for advice both during and after hours.

Patients from regional centres should be assigned a local consultant paediatrician and healthcare team to support shared care locally and maintain compliance support.

Step 5: Care after completing therapy and survivorship

5.1 Coming off treatment and surveillance in CNS tumours

All patients should have a dedicated consultation with their primary oncologist at the end-of-treatment. Where applicable, this consultation should also be timed with their neurosurgeon, clinical nurse consultant and clinical trials coordinator.

At the end-of-treatment consultation, all patients will receive a treatment summary, copies of which should be sent to the patient's GP and, where applicable, the paediatrician. The treatment summary should include:

- the site of the tumour within the CNS and histological diagnosis (as well as any molecular classifications and other relevant testing performed, both tumour and germline)
- the date and type of any neurosurgical procedures (for example, partial or gross resection) including the patient's age at the time of surgery
- the date of diagnosis
- the treatment protocol (if applicable)
- all treatments delivered, including the commencement and completion dates
- chemotherapy (as applicable) including agents administered and dosages
- radiotherapy (as applicable) including all radiation fields, total radiation dose to each field and the patient's age at the first dose of radiation
- significant morbidities or adverse events experienced during treatment
- contacts at each relevant specialty service where treatment was undertaken.

Surveillance management in CNS tumours

Determinants for managing the timing and period of surveillance for CNS tumours include the tumour biology, growth, location, treatment and traditional patterns of recurrence. Surveillance following treatment for a CNS tumour includes a complete physical examination and history, neurological examination, visual acuity and imaging. Other tests and investigations will be tailored to the patient, their prior treatment and tumour type. For patients enrolled on clinical trials, surveillance will be also determined by the requirements of the clinical trial protocol.

Following treatment, surveillance requires more than monitoring for tumour recurrence. Children treated for CNS tumours have a high-risk of long-term effects of treatment. Interventions required in recognising and treating the early and late complications of disease and treatment should be incorporated into the surveillance roadmap and not delayed until entry into a survivorship service. This includes interventions in neuropsychology, psychosocial and educational supports, endocrinology and persisting neurological sequelae.[111]

At the end-of-treatment consultation, all patients should be provided with a tailored surveillance roadmap, including timings for clinical reviews, tests and investigations required following completion of treatment. The roadmap should also be sent to the patient's GP and, if applicable, to the paediatrician. The roadmap will also incorporate timings for interventions that are tailored to the individual, to provide early interventions in managing the late effects of treatment.

Surveillance imaging

Optimal time intervals and the length of surveillance imaging for children and adolescents who have completed treatment for CNS tumours are often varied and sometimes lack consensus, particularly in screening for asymptomatic relapse.[151,153] Routine imaging also comes with a degree of risk, including the use of general anaesthesia in young patients, the negative psychological impact of testing on the patient and family and the overall costs to the health service.[154]

The level five and six paediatric cancer services should develop standardised, state-wide medical imaging surveillance protocols for all CNS tumours (clinical trial demands may override or complement these timings). Considerations should include:

- MRI as the standard imaging technique, avoiding the use of CT
- initiatives that reduce the need for general anaesthesia in young children
- scheduling based on tumour biology, risk stratification, growth and patterns of recurrence
- reducing the burden of travel for imaging for regional and remote families

Continued next page

- consistency of MRI sequences (protocols), particularly across shared care sites
- the use of image-sharing software across sites for comparison reporting
- basing timings and length of surveillance imaging on the available evidence
- being consistent with the ALARA (As Low as Reasonably Achievable) principles of medical imaging.

5.2 Survivorship

Childhood survivors of CNS tumours are at high-risk of late effects and experience poorer health-related quality of life than healthy comparators and other childhood cancer survivors.[155,156] In particular, the impaired neurocognitive consequences of treatment described,[157,158] as well as increased risk for neurovascular disease, second cancers and endocrinopathies,[159] demand a more tailored approach.

The survivorship program.

The survivorship program should ideally have a neuro-oncology clinical service that includes representation or access to:

- medical oncology with a subspecialty in childhood cancer survivorship
- school education, with experience in childhood cancer
- paediatric oncology nursing with a subspecialty in childhood cancer survivorship
- paediatric endocrinology
- psychology, with a subspecialty in childhood cancer survivorship
- social work, with experience in childhood cancer
- physio, occupational and speech therapy
- reproductive health.

Where rehabilitative services have been introduced during treatment, their work should continue alongside or within the survivorship service while there is still a demonstrable effect of their interventions on the child and family. Consultation with neurosurgery and radiation oncology should be maintained.

All survivors of childhood CNS tumours should be referred to an appropriate survivorship program within three months of completing treatment to formulate a shared care plan between the acute and survivorship services.

All patients should be given an updated treatment summary and roadmap for late effects surveillance on entering the survivorship program. The roadmap should also be sent to the child's GP and, when applicable, the paediatrician.

Patients and their families should also be provided with educational material about survivorship, including adopting a healthy lifestyle and education bridging programs for school.

5.3 Transition from paediatric to adult care

A general discussion for transition is provided in the 'fundamentals of care' section of this document.

From a CNS tumour perspective, treatment protocols continue to aim to reduce morbidity; however, this cohort still remains at high-risk of late effects and the need for supported transition is magnified for child and adolescent survivors of CNS tumours.[160] Some of this care may exceed the abilities and scope of primary care practice. The patient will often move from a paediatric multidisciplinary neuro-oncology environment to a fragmented adult service.[161] Transition of patients with high-risk, chronic health needs may benefit from a joint care model, with the first or initial visits including the paediatric and adult service.[160] Both the adult and paediatric health service will need to develop relationships to be able to collect outcome data on adult survivors of CNS tumours,[156] as well as being a resource for adult services for ongoing support.[162]

Transition of adult survivors of childhood CNS tumours with actual or a high-risk of late effects that require services beyond primary care should be referred to adult speciality facilities. This may include, but not be limited to, adult endocrinology, neurology, vascular, rehabilitative and psychology services.

All CNS tumour survivors with VP shunts in situ should be referred either to their primary neurosurgeon or to an adult neurosurgeon at transition for annual review.

Joint care models to transition from paediatric to adult services require effective two-way communication and information sharing and should be developed as a standard of care.

All correspondence and planning should also be sent to the patient's GP.

Step 6: Managing refractory disease or relapse

The risk of relapse/recurrence and refractory disease in childhood CNS tumours is relative to factors such as the tumour site and pathology, extent of resection, age and previous treatment.[110] Some tumours such as diffuse midline gliomas still remain refractory to treatment and have a poor prognosis.[163] For many malignant tumour types, such as ependymoma[164] and medulloblastoma,[124] outcomes following relapse are poor. For others, such as pilocytic astrocytoma, disease recurrence may be managed effectively with surgery or chemotherapy.[125] Disease progression or recurrence is usually at the primary site and can often occur years after diagnosis.[165] Tumours of the CNS are associated with the highest incidence of late mortality in childhood cancer survivors, primarily due to recurrence or progression of disease.[166]

6.1 Signs and symptoms

Most signs and symptoms of relapse or disease progression will be noted during routine clinical evaluation or medical imaging; these are diverse and relative to the tumour type and location, as well as the patient's age.

6.2 Multidisciplinary team

There should be an immediate referral to a state-wide paediatric neuro-oncology MDM, as well as a psychosocial referral, for the discussion and management of all children with suspected or confirmed relapse and/or disease progression.

6.3 Treatment

There are few curative management options for most children and adolescents with high-grade tumours who experience recurrence, particularly where gross total resection can't be achieved and/or radiotherapy has already been used as the standard of upfront care. However, due to the rapidly changing molecular landscape, there are more targeted therapies and early-phase clinical trials emerging[110] and the level five or six paediatric cancer services should be responding to this by supporting the opening of these trials.

A complete evaluation of the extent of relapse should be undertaken upfront. This is dependent on tumour type and may be limited to imaging but may also include surgery, lumbar puncture and bone marrow biopsy.

Consideration should be made for molecular characterisation of tissue biopsy at the time of relapse where the state-wide paediatric neuro-oncology MDM had identified the potential for actionable targeted therapy.[113] Ideally this will be performed on the relapse sample and within the shortest possible timeframe comparable with best practice international criteria.

The exact nature of the relapse/progression and prospective treatment plan should be shared with the family and, where applicable, the child/adolescent following the state-wide paediatric neuro-oncology MDM. Recommendations from the state-wide neuro-oncology MDM should be communicated with the patient's GP and, where appropriate, their paediatrician or local shared care health service.

As treatment for relapse in high-grade CNS tumours is often about prolonging life rather than cure, the nature and intentions of therapy should be clearly defined to support both the patient and family's decision making. This may still include interventions such as chemotherapy and/or radiotherapy. Participation in active interventions should not preclude involving a palliative care service. As many families will seek alternate opinions at this point in time, it is important that the MDT has carefully considered

options, that these options are discussed with the family, that decisions are made in the best interests of the child and that decisions are communicated to the wider treating team and documented.

6.4 Palliative care

Patients with an uncertain prognosis and/or high symptom burden should be able to access palliative care services alongside any therapies. The principles of a palliative care approach need to be documented and shared with the team. The decision should be made in collaboration with the child or adolescent, and their family.

A palliative care service referral should be undertaken and documented for all patients when there is no longer a curative regimen available, either at the time of diagnosis or at the time of relapse or disease progression.

Consideration for a referral to palliative care service should be made for all other patients at the time of relapse or disease progression.

Discussions and documentation of advance care planning should begin during this period and be guided by evidence-based policy, guidance and frameworks such as the Victorian Government's *Thinking ahead framework: planning care for children with life-limiting conditions.*[167-169]

The advance care plan should be tailored to the patient's disease and location of the tumour to guide the potential side effect profile and management strategies. This should also be accompanied by tailored, anticipatory guidance for the family.

More information around palliative care can be found in the 'fundamentals of care' section.

Step 7: End-of-life care

Step 7 is concerned with maintaining the child or adolescent's quality of life and addressing their health and supportive care needs, as well as the needs of the family, at the end-of-life.

7.1 Symptoms at the end-of-life and advance care planning

The end-of-life period for children and adolescents with CNS tumours can often be associated with a high symptom burden[170] and can still be a period of active medical care.[171] Symptoms are often relative to the location of the tumour and can include paralysis, cognitive deterioration, behavioural changes, dysphagia, dysarthria and dysphasia.[170,171] These neurological deficits can rapidly intensify at the end-of-life. From a psychosocial viewpoint, the loss or deterioration in communication has been described as a significant turning point for families of children with CNS malignancies.[172]

Elements of end-of-life care should be in line with the Australian Commission on Safety and Quality in Health Care document *National Consensus Statement: essential elements for safe and high-quality paediatric end-of-life care.*[51]

An advance care plan specific to end-of-life care should be documented early in this stage.

There should be 24-hour on-call support, directed by the palliative care team, for families who choose for their child to die at home.

More information around end-of-life care can be found in the 'fundamentals of care' section.

7.2 Cancer research at the end-of-life

At the end-of-life, many resistant tumours, such as diffuse midline gliomas, that have led to death may not have been biopsied.[111] Autopsy samples allow the researcher to obtain important information from some of the most aggressive types of tumours, from multiple sites and in larger samples[111, 173] Families who have consented to autopsy of their child in the context of CNS tumour research have been shown to achieve a positive feeling of altruism, and do not regret their decision.[173,174]

The level five and six cancer services should consider collecting autopsy samples of rare and resistant CNS tumours for research that are guided by evidence-based ethical and clinical governance. Timing of discussions for consent should occur well before the child's death, with clear and concise information shared with the parent/caregiver about the autopsy process and use of tissue.

Ongoing commitment to continuous improvement in the treatment of CNS tumours

Other key strategies for health services to consider include:

- continued collaboration with research institutions in discovering key pathways and genetic changes of CNS tumour initiation and maintenance
- improving risk stratification through establishing biologically-defined subgroups
- reducing the incidence of long-term toxicities of treatment
- improving the discovery and development of molecularly-targeted therapies and novel routes of administration
- encouraging multisite collaborative research and discussion of patients, particularly in managing rare subgroups
- emphasising the importance of supportive and rehabilitative care throughout treatment and into survivorship
- incorporating data from standardised neuropsychology assessments into a collaborative national dataset to assist research into evaluation and interventions[122]
- supporting active surveillance and recording of metastatic and non-malignant brain tumours in children and adolescents in cancer registries to inform the planning of healthcare services and resource allocation for this patient population[95]
- examining the use of intraoperative MRI, which may be of benefit to increase the extent of tumour resection[137, 175,176] (however, at this point in time, the quality of the evidence remains low and further research is required)[177,178]
- other technologies or techniques that augment the field of vision, improve resection or facilitate delivery of therapy, such as robot-assisted surgery, laser surgery and convection-enhanced delivery of chemotherapy[137]
- being able to gain a greater understanding of the tumour 'in vivo' through exploring new technologies and techniques in medical imaging.[99] The use of molecular imaging is likely to play a greater role in the era of precision medicine and targeted therapies and should be encouraged as a standard of care into the future when clinically applicable.[179]

Glossary

Advance care planning

A process of discussing future medical treatment and care based on an individual's preferences, goals, beliefs and values, which can guide future decisions should the person become unable to communicate.

Child/adolescent

The Children, Youth and Families Act 2005 defines childhood (including adolescence) as the period from 0 to 17 years. The World Health Organization defines adolescents as individuals aged 10–19 years. The paediatric oncology care pathway is intended as a resource in managing children and adolescents diagnosed with cancer from birth to 18 years of age.

Consumer

A term that can refer to people affected by cancer, patients and potential patients, carers, organisations representing cancer consumer interests, members of the public who are targets of cancer promotion programs and groups affected in a specific way as a result of cancer policy, treatment or services.

Cultural and linguistic diversity

Refers to the range of different cultures and language groups represented in the population who identify as having particular cultural or linguistic affiliations by virtue of their place of birth, ancestry or ethnic origin, religion, preferred language or language spoken at home.

End-of-life care

A distinct phase of palliative care, appropriate when a patient's symptoms are increasing and functional status is declining despite anti-cancer therapy.

Family

The patient, their carers and relatives. Family may include parents, siblings, other relatives, guardians and friends.

Level five paediatric cancer service

A level five service provides state-wide, national and international leadership in paediatric oncology, including research, clinical guidance, education and policy development. A level five service will also assess and manage risk in new therapies and supportive care interventions, providing leadership and planning for other service levels. A level five service is recognised as a primary treatment centre and will provide diagnostic services and/or management of at least 30 new cancer patients per year. A level five service will provide comprehensive care for the majority of paediatric oncology presentations within its catchment area, with direct links to a level six service.

Level six paediatric cancer service

As per level five, as well as being as a state-wide referral centre for paediatric oncology, a level six service will provide diagnostic services and/or management of at least 100 diagnoses per year from the local catchment as well as referrals from other geographical regions.

Multidisciplinary meeting (MDM)

A regularly scheduled meeting of core and invited team members of the health service for the purpose of prospective treatment and care planning of newly diagnosed cancer patients as well as those requiring a review of their treatment plan or palliative care.[94]

Multidisciplinary team (MDT)

Comprises the core disciplines integral to providing good care. The team is flexible in approach, reflects the patient's clinical and psychosocial needs and has processes to facilitate good communication.

Oncology care pathway

The key principles and practices required at each stage of the care pathway to guide the delivery of consistent, safe, high-quality and evidence-based care.

Palliative care

Any form of medical care or treatment that concentrates on reducing the severity of disease symptoms.

Primary oncologist

The clinician who has lead responsibility for managing the patient's cancer care. The lead clinician may change over time depending on the stage of the care pathway and where care is being provided.

Rehabilitation

Comprises multidisciplinary efforts to allow the patient to achieve optimal physical, social, physiological and vocational functioning within the limits imposed by the disease and its treatment.

Shared care

The establishment of pathways through which clients and health professionals in hospital and community settings can collaborate in developing a therapeutic plan that meets the clinical and functional needs of the client.

Surveillance

Period of time the healthcare team is looking for signs of relapse and monitoring side effects of treatment for cancer.

Survivorship

Period beyond surveillance where the healthcare team is looking at the potential late effects of treatment for cancer.

Telehealth

Healthcare delivery or related activities (such as education) when some of the participants are separated by distance and information and communications technologies are used to overcome that distance.

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Fundamentals of care and acute leukaemia

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