

# Appendix B

## SURVIVORS OF ALLOGENEIC BONE MARROW TRANSPLANTATION

Long-term survivors of paediatric bone marrow transplantation (BMT) are at high risk of late adverse effects of treatment. This is due in part to the intensive and high dose nature of treatment, often including radiotherapy (RT), received as part of the BMT process, and in part to the fact that many BMTs are performed for poor prognosis disease. Such patients have already received a great deal of treatment before BMT, involving several cytotoxic drugs and frequently RT. Although BMT is felt to offer the best chance of cure in these children and adolescents, it is acknowledged that considerable late toxicity may be inevitable in a relatively high proportion of patients. Therefore, it is important that survivors of BMT undergo follow up in a setting that allows adequate opportunity for careful review of their physical, mental and psychological health, with recognition and appropriate management of any adverse effects. Nearly all of the published literature about the occurrence of late adverse effects after haemopoietic stem cell transplantation describes patients who have received bone marrow as a source of stem cells rather than peripheral blood or umbilical cord blood, but it is likely that the profile of adverse effects will be broadly similar after these newer techniques due to the significant causative role of prior and conditioning treatment toxicity.

Most of the adverse effects of prior and conditioning chemotherapy and RT in paediatric BMT recipients are the same as those seen in children receiving the same treatment in the non-BMT setting, and are not covered in detail in this section (being cross-referenced instead to other system or site specific sections in this Statement). Nevertheless careful follow up is needed since high treatment doses and / or additive effects may lead to unusual or accentuated toxicity. In addition, survivors of paediatric allogeneic BMT are also at risk of a range of severe and potentially life-threatening manifestations of chronic graft versus host disease (cGvHD), other immune-mediated disturbances (eg haematological cytopenias), and delayed immune reconstitution. A high index of suspicion is needed to enable early detection and optimal management of these complications.

Clinical investigation is complicated by the knowledge that there is a very wide range of severity of clinical abnormalities seen after BMT. Furthermore, it may be unclear whether early diagnosis and perhaps treatment of subclinical toxicity improves the outcome. Unfortunately, the detailed prospective and longitudinal research necessary to understand the true significance of subclinical abnormalities is seldom available.

Table I summarises the characteristics, causes of and higher risk factors for late adverse effects of paediatric BMT, followed by recommendations for clinical assessment, and initial further action that may be required. For each system or site, it is indicated whether routine evaluation (as described in Table I) is required in the absence of overt symptoms, or whether it is only needed in the presence of certain symptoms or signs.

**In general, most of the long term follow up evaluations specified in Table I may be carried out in the context of annual reviews, as indicated by the statement “At Long Term Follow Up clinic” in the Frequency column (see footnote d). Table II provides a suggested checklist for quick reference at such reviews. Some units may wish to perform additional investigations in patients receiving BMT for specific or rarer indications. However, an increased frequency of assessment is appropriate in some circumstances, notably during adolescence in view of the need to monitor growth and pubertal development every 3 - 6 months, and also in patients with significant complications (eg active cGvHD) and in patients still within 5 years of transplant.** Although the risk of developing a new onset of some late adverse effects decreases with very long term follow up (eg in TBI recipients, the chance of developing primary hypothyroidism for the first time diminishes once more than 10 years post-BMT), this is not true for some other complications (eg secondary malignancies, where the risk continues to increase with time). Nevertheless, once a patient is 10 years post-BMT and at final height, it may be possible to reduce the frequency of follow up to every two years in carefully selected cases. Notwithstanding the above comments, there is very little clear published evidence concerning the optimum frequency of evaluation, and it is recognised that this will vary according to clinical and local organisational factors. Therefore, few defined intervals of evaluation are suggested in Table I, and those that are specified should be regarded as pragmatic suggestions based on clinical experience and expert opinion, rather than high grade recommendations.

As for the Practice Statement as a whole, the information in both Tables is intended to help and guide busy clinicians, but not to replace clinical judgement nor to be prescriptive.

**TABLE 1 - LATE ADVERSE EFFECTS OF BONE MARROW TRANSPLANTATION**

SYSTEM • OUTCOMES	CAUSES <sup>a</sup>	CLINICAL EVALUATION <sup>c</sup>	FURTHER ACTION <sup>c,f</sup>
	HIGHER RISK FACTORS <sup>b</sup>	FREQUENCY OF FOLLOW UP <sup>c,d,e</sup>	
<b>Quality of Life</b> Functional impairment <ul style="list-style-type: none"> <li>• Family, social</li> <li>• Emotional, relationships</li> <li>• Education, employment</li> <li>• Sexual relationships</li> </ul>	<ul style="list-style-type: none"> <li>• Any treatment</li> </ul>	Routine evaluation needed even in absence of overt symptoms <i>See Quality of Life</i>	See <i>Quality of Life</i>
	<ul style="list-style-type: none"> <li>• Chronic complications, especially cGvHD</li> </ul>	At Long Term Follow Up clinic	
<b>Secondary Malignancy</b> <ul style="list-style-type: none"> <li>• Solid tumours – especially brain, thyroid, oral / salivary gland, skin; typically later onset (median 4-8 yrs post-BMT)</li> <li>• AML / MDS – predominantly after autologous BMT, very rare in children; usually earlier onset (median 2.5 yrs post-BMT)</li> </ul>	<ul style="list-style-type: none"> <li>• Radiotherapy (RT), including TBI (→ solid tumours)</li> <li>• Chemotherapy, particularly alkylating agents and topoisomerase II inhibitors (especially epipodophyllotoxins) (→ AML / MDS)</li> <li>• Immunosuppressive treatment</li> <li>• Familial cancer predisposition syndromes, including Fanconi anaemia</li> </ul>	Routine evaluation needed even in absence of overt symptoms <i>See Secondary Malignancy</i>	See <i>Secondary Malignancy</i>
	<ul style="list-style-type: none"> <li>• Young age</li> <li>• Cranial / craniospinal RT</li> <li>• High RT dose</li> <li>• cGvHD</li> </ul>	At Long Term Follow Up clinic	
<b>Haematology</b> <ul style="list-style-type: none"> <li>• Immune-mediated cytopenia</li> </ul>	<ul style="list-style-type: none"> <li>• Any allogeneic BMT</li> </ul>	Routine evaluation needed even in absence of overt symptoms 1) Symptoms and signs of bone marrow dysfunction 2) FBC	1) Further investigation as appropriate 2) Consider immunosuppression (eg steroids) and / or immunomodulation (eg IVIg)
	<ul style="list-style-type: none"> <li>• cGvHD</li> </ul>	At Long Term Follow Up clinic	
<b>Immunology</b> <ul style="list-style-type: none"> <li>• Delayed immune reconstitution → increased risk of infection</li> <li>• Auto-immune disease (often associated with cGvHD) - hypo- and hyperthyroidism, myasthenia gravis, diabetes, hepatitis</li> </ul>	<ul style="list-style-type: none"> <li>• Any allogeneic BMT</li> <li>• Prolonged immunosuppression</li> </ul>	Routine evaluation needed even in absence of overt symptoms 1) Discuss risk, advise about appropriate responses to symptoms of infection 2) Immune function tests – immunoglobulins, lymphocyte subsets (especially CD4) 3) Further investigation may include auto-antibodies, endocrine function tests, LFTs, where appropriate	1) Anti-infective prophylaxis, including IVIg, during risk period; long term antibiotics (eg penicillin V) recommended in TBI recipients 2) Infection surveillance 3) Reimmunisation as appropriate (see also <i>Appendix E, Immunisation after completion of treatment</i> ) 4) Referral to Immunologist or Endocrinologist as appropriate
	<ul style="list-style-type: none"> <li>• Mismatched donor BMTs</li> <li>• Unrelated donor BMTs</li> <li>• cGvHD</li> </ul>	At Long Term Follow Up clinic	

SYSTEM	CAUSES	CLINICAL EVALUATION	FURTHER ACTION
• OUTCOMES	HIGHER RISK FACTORS	FREQUENCY OF FOLLOW UP	
<p><b>Chronic GvHD (cGvHD)</b></p> <ul style="list-style-type: none"> <li>• Secondary malignancy — especially of oral cavity or skin</li> <li>• Haematology — see above</li> <li>• Immunology — see above</li> <li>• Visual — keratoconjunctivitis sicca</li> <li>• Oral — xerostomia, lichenoid or atrophic lesions</li> <li>• Respiratory — obstructive airways disease</li> <li>• Gastrointestinal — nausea, vomiting, oesophageal stricture, diarrhoea, intestinal or pancreatic malabsorption</li> <li>• Hepatic — cholestatic damage</li> <li>• Renal — proteinuria, nephrotic syndrome</li> <li>• Peripheral nervous system — neuropathy, myasthenia gravis, vasculitic syndromes</li> <li>• Musculoskeletal — polymyositis, sclerodermatous joint contractures</li> <li>• Skin — lichenoid or sclerodermatous lesions</li> <li>• Serosal — effusions (pleural, pericardial, peritoneal)</li> <li>• Adverse effects of immunosuppressive treatment — eg steroids, cyclosporin A</li> </ul>	<p>Any allogeneic BMT</p>	<p>Routine evaluation needed even in absence of overt symptoms</p> <ol style="list-style-type: none"> <li>1) Thorough history and clinical examination</li> <li>2) High index of suspicion, especially in higher risk patients</li> </ol>	<ol style="list-style-type: none"> <li>1) Further investigations as clinically indicated</li> <li>2) Immunosuppressive and / or immunomodulatory treatment as clinically indicated</li> <li>3) Caution regarding adverse effects of immunosuppressive treatment, especially increased risk of infection (see <i>Immunology</i> above)</li> <li>4) Consider reimmunisation with non-live vaccines in patients not on IVIg, but avoid live vaccines (see also <i>Appendix E, Immunisation after completion of treatment</i>)</li> <li>5) Refer to other specialists eg Respiratory as clinically indicated</li> </ol>
	<ul style="list-style-type: none"> <li>• Mismatched donor BMTs</li> <li>• Unrelated donor BMTs</li> <li>• Older patient age at BMT</li> </ul>	<p>At Long Term Follow Up clinic</p>	

SYSTEM • OUTCOMES	CAUSES HIGHER RISK FACTORS	CLINICAL EVALUATION FREQUENCY OF FOLLOW UP	FURTHER ACTION
<p><b>Visual</b></p> <p><u>Anterior segment</u></p> <ul style="list-style-type: none"> <li>• Posterior subcapsular cataract</li> <li>• Keratoconjunctivitis sicca → corneal / conjunctival ulceration / scarring</li> </ul> <p><u>Posterior segment</u></p> <ul style="list-style-type: none"> <li>• Chorioretinitis</li> </ul>	<ul style="list-style-type: none"> <li>• RT to field including eyes (including TBI)</li> <li>• ?Chemotherapy</li> <li>• Steroids</li> <li>• Infection – chorioretinitis (viral, toxoplasmosis)</li> <li>• High RT dose / dose rate</li> <li>• Unfractionated TBI</li> <li>• Prolonged steroid use (cataract)</li> <li>• cGvHD – associated with keratoconjunctivitis sicca</li> </ul>	<p>Routine evaluation needed even in absence of overt symptoms</p> <ol style="list-style-type: none"> <li>1) History and examination – vision, dryness or discomfort of eyes, photophobia</li> <li>2) High index of suspicion for cGvHD in patients with keratoconjunctivitis sicca – look carefully for other features</li> </ol> <p>See also <i>Visual</i></p> <p>At Long Term Follow Up clinic See <i>Visual</i></p>	<ol style="list-style-type: none"> <li>1) Refer to Ophthalmologist for assessment of symptoms or abnormal clinical signs</li> <li>2) Review immunosuppressive treatment in keratoconjunctivitis sicca associated with cGvHD</li> </ol> <p>See also <i>Visual</i></p>
<p><b>Auditory</b></p> <ul style="list-style-type: none"> <li>• Sensorineural hearing impairment</li> <li>• Impaired speech development</li> </ul>	<ul style="list-style-type: none"> <li>• Chemotherapy – platinum agents (cisplatin &gt; carboplatin)</li> <li>• Younger age increases risk of impaired speech development</li> <li>• Higher platinum dose</li> <li>• RT to field including ears – if given prior to platinum</li> <li>• Other ototoxic drugs - especially aminoglycosides</li> </ul>	<p>Routine evaluation needed even in absence of overt symptoms</p> <p>See <i>Auditory</i></p> <p>At Long Term Follow Up clinic See <i>Auditory</i></p>	<p>See <i>Auditory</i></p>
<p><b>Craniofacial / dental, oral</b></p> <p><u>Craniofacial / dental</u></p> <ul style="list-style-type: none"> <li>• Impaired craniofacial skeletal growth</li> <li>• Dental abnormalities, including root, enamel</li> </ul> <p><u>Oral</u></p> <ul style="list-style-type: none"> <li>• Reduced saliva → xerostomia, difficulty in mastication and swallowing</li> <li>• Lichenoid lesions / leukoplakia</li> <li>• Oral / salivary gland tumours</li> </ul>	<ul style="list-style-type: none"> <li>• RT to field including jaw (including TBI, cranial)</li> <li>• Chemotherapy</li> <li>• cGvHD</li> <li>• Young age at treatment</li> <li>• Prior RT (ie before BMT)</li> <li>• cGvHD</li> </ul> <p><b>NB</b> Both TBI and cGvHD may contribute to xerostomia and development of tumours</p>	<p>Routine evaluation needed even in absence of overt symptoms</p> <ol style="list-style-type: none"> <li>1) History and examination – suspicious intraoral lesions</li> <li>2) Educate family re importance of regular dental examination</li> <li>3) High index of suspicion for cGvHD in patients with suspicious oral lesions – look carefully for other features</li> </ol> <p>See also <i>Craniofacial / Dental</i></p> <p>At Long Term Follow Up clinic See <i>Craniofacial / Dental</i></p>	<ol style="list-style-type: none"> <li>1) Liaise closely with family and hospital dentists</li> </ol> <p>See also <i>Craniofacial / Dental</i></p>

SYSTEM	CAUSES	CLINICAL EVALUATION	FURTHER ACTION
<p><b>• OUTCOMES</b></p> <p><b>Endocrine / growth</b></p> <ul style="list-style-type: none"> <li>• Pituitary – GH deficiency → growth impairment → short stature, skeletal disproportion, reduced BMD, adult GH deficiency syndrome</li> <li>• Thyroid – hypothyroidism, hyperthyroidism (rare), autoimmune disease, benign and malignant tumours</li> <li>• Adrenal – hypoadrenalism rarely observed unless prolonged steroid treatment</li> <li>• Pancreas - metabolic syndrome (hyperinsulinaemia, impaired glucose tolerance, hyperlipidaemia, ±hypertension, ±obesity), diabetes mellitus</li> </ul>	<p><b>HIGHER RISK FACTORS</b></p> <ul style="list-style-type: none"> <li>• RT to field including affected gland (TBI, TL, cranial, craniospinal, thyroid, neck, mantle, mediastinum, ?abdominal [pancreas])</li> <li>• Chemotherapy, including busulphan and cyclophosphamide</li> <li>• Steroids (growth impairment)</li> </ul>	<p><b>FREQUENCY OF FOLLOW UP</b></p> <p>Routine evaluation needed even in absence of overt symptoms</p> <p><u>Growth</u> See also <i>Hypothalamic Pituitary Axis</i></p> <ol style="list-style-type: none"> <li>1) Measure height (including sitting height) and weight, calculate height velocity</li> <li>2) Measure IGF-1 and bone age in TBI recipients if concern about growth (in liaison with Endocrinologist)</li> </ol> <p><u>Thyroid</u> See also <i>Thyroid</i></p> <ol style="list-style-type: none"> <li>1) Measure TFTs (T<sub>4</sub>, TSH)</li> <li>2) Palpate thyroid gland</li> </ol> <p><u>Pancreas</u></p> <ol style="list-style-type: none"> <li>1) Symptoms and signs of pancreatic endocrine dysfunction</li> <li>2) Perform urinalysis for glycosuria</li> <li>3) Measure fasting blood glucose, fasting lipids, HbA<sub>1c</sub></li> </ol> <p><b>NB</b> Consider referral to Endocrinologist in all BMT recipients, but especially those who have received TBI or busulphan-based conditioning</p> <p>At Long Term Follow Up and Endocrine clinics</p>	<p><b>Growth</b> See also <i>Hypothalamic Pituitary Axis</i></p> <ol style="list-style-type: none"> <li>1) Refer to Endocrinologist for consideration of dynamic GH testing in TBI recipients with slow growth (height velocity &lt;25th centile) and assessment of requirement for GH treatment</li> </ol> <p><u>Thyroid</u> See also <i>Thyroid</i></p> <ol style="list-style-type: none"> <li>1) Discuss with / refer to Endocrinologist re thyroxine treatment if compensated or overt hypothyroidism (on 2 successive TFTs measurements for compensated hypothyroidism)</li> <li>2) Measure thyroid autoantibodies if TFTs abnormal</li> <li>3) Perform ultrasound scan of neck if thyroid nodule palpated, and refer to Endocrinologist / Surgeon for fine needle biopsy</li> </ol> <p><u>Pancreas</u></p> <ol style="list-style-type: none"> <li>1) Perform glucose tolerance test if fasting glucose elevated</li> <li>2) Refer to Endocrinologist for management of diabetes or metabolic syndrome</li> </ol>

SYSTEM • OUTCOMES	CAUSES HIGHER RISK FACTORS	CLINICAL EVALUATION FREQUENCY OF FOLLOW UP	FURTHER ACTION
<b>Gonadal / Reproductive</b> <ul style="list-style-type: none"> <li>Female</li> <li>Male</li> </ul> <p><b>Female</b></p> <ul style="list-style-type: none"> <li>Ovarian failure – delayed / arrested puberty, amenorrhoea, impaired fertility, increased risk of adverse pregnancy outcome, early menopause</li> </ul>	<ul style="list-style-type: none"> <li>RT to field including gonads (and uterus)</li> <li>Chemotherapy, especially alkylating agents (see list in <i>Gonadal</i> – Female, Male)</li> </ul> <p><b>Female</b></p> <ul style="list-style-type: none"> <li>Older age at BMT</li> <li>High total RT dose to gonads and uterus</li> <li>Unfractionated TBI</li> <li>High dose of alkylating agents</li> </ul>	<p><b>Female and Male</b></p> <p>Routine evaluation needed even in absence of overt symptoms</p> <ol style="list-style-type: none"> <li>Assess pubertal (Tanner) stage, including testicular examination (?soft) and volume (using orchidometer), in context of age and linear growth</li> <li>Measure sex hormones (testosterone or oestrogen), gonadotrophins (FSH, LH) and inhibin B (if available) from approximately 10 years of age (<b>NB</b> Measurement of gonadotrophins unhelpful in pre-pubertal children)</li> <li>Semen analysis when appropriate</li> <li>Discuss risk of impaired fertility, adverse pregnancy outcome, early menopause</li> <li>Advise that contraception is still advisable in view of possibility (albeit uncommon) of fertility</li> </ol> <p>See also <i>Gonadal</i> – Female, Male</p>	<ol style="list-style-type: none"> <li>Refer to Endocrinologist for assessment of requirement for hormone replacement treatment in patients with Leydig cell or ovarian failure</li> <li><b>NB In females on hormone replacement treatment, consider trial off treatment at appropriate intervals (eg 4 yearly) to evaluate possible ovarian recovery</b></li> <li>Discuss referral to Reproductive Medicine specialist for consideration of assisted reproduction technology in appropriate situations</li> </ol> <p>See also <i>Gonadal</i> – Female, Male</p>
<p><b>Male</b></p> <ul style="list-style-type: none"> <li>Germ cell failure - impaired fertility</li> <li>Leydig cell dysfunction - delayed / arrested puberty</li> <li>Erectile dysfunction</li> </ul> <p><b>NB</b> Germ cell much commoner than Leydig cell failure</p>	<p><b>Male</b></p> <ul style="list-style-type: none"> <li>Younger age at BMT (Leydig cell dysfunction)</li> <li>High total RT dose to gonads</li> <li>High dose of alkylating agents</li> </ul>	<p><b>Female and Male</b></p> <p>At Long Term Follow Up and Endocrine clinics</p> <ol style="list-style-type: none"> <li>Assessment of pubertal stage and growth at least every 3-6 months until completion of puberty and growth</li> <li>Measurement of sex hormones and gonadotrophins annually</li> </ol> <p><b>NB</b> Testicular volume is reduced in boys with germ cell failure, and is therefore not a reliable indicator of pubertal progression</p>	<p>See also <i>Gonadal</i> – Female, Male</p>
<p><b>NB Ovarian recovery</b> is well documented, but <b>recovery of spermatogenesis</b> rare with most classic BMT conditioning regimens. Some lower dose regimens may have higher gonadal recovery rates.</p> <p><b>Neurological (CNS, PNS, spinal)</b></p> <ul style="list-style-type: none"> <li>Leucoencephalopathy</li> <li>Vasculopathy – CVAs, vasculitis, 'migraine-like' episodes</li> <li>CNS infections</li> <li>Benign and malignant CNS tumours</li> <li>Peripheral neuropathy (thaliadomide – predominantly sensory → paraesthesia, numbness)</li> </ul>	<ul style="list-style-type: none"> <li>RT to field involving brain (TBI, cranial, craniospinal)</li> <li>Chemotherapy – methotrexate (systemic or intrathecal)</li> <li>Immunosuppressive treatment – thaliadomide (peripheral neuropathy)</li> <li>High cumulative RT dose (leucoencephalopathy, tumours)</li> <li>cGVHD (vasculitis)</li> <li>Prolonged immunosuppression (CNS infection)</li> </ul>	<p>Routine evaluation needed even in absence of overt symptoms</p> <ol style="list-style-type: none"> <li>History and examination – especially headaches, raised intracranial pressure, cranial nerve and motor function, gait, peripheral nerve function</li> <li>High index of suspicion, especially in higher risk patients</li> </ol> <p>See also <i>Neurological</i></p> <p>At Long Term Follow Up clinic See <i>Neurological</i></p>	<ol style="list-style-type: none"> <li>Further investigation and treatment as appropriate, depending on clinical event</li> </ol> <p>See also <i>Neurological</i></p>

SYSTEM		CAUSES		CLINICAL EVALUATION		FURTHER ACTION	
• OUTCOMES		HIGHER RISK FACTORS		FREQUENCY OF FOLLOW UP			
<p><b>Neuropsychological</b></p> <ul style="list-style-type: none"> <li>• Functional impairment</li> <li>• Cognitive impairment</li> </ul>		<ul style="list-style-type: none"> <li>• RT to field involving brain (TBI, cranial, craniospinal)</li> <li>• Chemotherapy – methotrexate (systemic or intrathecal), busulphan</li> <li>• Young age (especially &lt;3 years) at treatment</li> <li>• Female gender</li> <li>• High cumulative RT dose</li> <li>• Short interval between two RT treatment courses</li> <li>• Longer duration of follow-up</li> </ul>		<p>Evaluation needed in response to symptoms or school difficulties</p> <p>1) History and examination – memory, attention, intelligence, visual-spatial, verbal and fine motor function, neurological deficit</p> <p>2) High index of suspicion, especially in higher risk patients</p> <p>See also <i>Neuropsychological</i></p> <p>At Long Term Follow Up clinic</p> <p><b>NB</b> Toxicity (especially cognitive impairment) may only become evident after prolonged follow-up</p>		<p>1) Liaise with school in all at risk patients</p> <p>2) Refer for Neuropsychological or Educational Psychological assessment in high risk patients or those with suspicious symptoms or signs – where appropriate, aim for Statement of Educational Needs and / or extra time in examinations</p> <p>See also <i>Neuropsychological</i></p>	
<p><b>Cardiovascular</b></p> <ul style="list-style-type: none"> <li>• Echocardiographic abnormalities</li> <li>• ECG abnormalities</li> <li>• Myocardial toxicity</li> <li>• Pericardial disease</li> <li>• Valvular disease</li> </ul>		<ul style="list-style-type: none"> <li>• Chemotherapy – mainly anthracyclines, but also high-dose cyclophosphamide, other alkylating agents</li> <li>• RT to field involving heart or mediastinum (including TBI)</li> <li>• Pre- / peri-BMT iron overload (eg thalassaemia, aplastic anaemia)</li> <li>• Sepsis</li> </ul>		<p>Routine evaluation needed even in absence of overt symptoms</p> <p>See <i>Cardiac</i></p>		<p>1) Advise against smoking</p> <p>See also <i>Cardiac</i></p>	
<p><b>Respiratory</b></p> <ul style="list-style-type: none"> <li>• Obstructive disease</li> <li>• Restrictive disease – ranging from isolated diffusion to classical restrictive defect</li> <li>• Late-onset pulmonary syndrome (with several underlying histologies, eg BO, BOOP, IP)</li> </ul>		<ul style="list-style-type: none"> <li>• Chemotherapy – especially bleomycin, busulphan, methotrexate, nitrosoureas</li> <li>• RT to field including lungs (including TBI, craniospinal, mediastinal, mantle)</li> <li>• cGVHD – associated with obstructive disease, may also exacerbate restrictive disease</li> <li>• Pulmonary infection – before, during or after BMT</li> <li>• Thoracic surgery may increase effects of pulmonary toxicity</li> </ul>		<p>Routine evaluation needed even in absence of overt symptoms</p> <p>1) History and examination – exercise tolerance, smoking</p> <p>2) Perform PFTs (see below)</p> <p>3) Consider CXR if symptomatic or if PFTs severely abnormal</p> <p>4) High index of suspicion for cGVHD, especially in higher risk patients – look carefully for other features</p> <p><b>NB</b> Patients are often asymptomatic even in the presence of severe pulmonary disease</p> <p>1) Perform CXR as indicated above</p> <p>2) Ideally perform baseline PFTs before BMT</p> <p>3) Repeat PFTs 1 year post-BMT (earlier if symptomatic)</p> <p>4) Repeat PFTs annually if abnormal or if new symptoms</p> <p>5) Repeat PFTs may be performed less frequently (eg 3-5 yearly) if asymptomatic and initial post-BMT PFTs normal</p>		<p>1) If symptomatic or if abnormal PFTs, a) refer to Respiratory specialist, b) consider high resolution CT scan</p> <p>2) Consider immunosuppressive treatment in chronic pulmonary disease associated with cGVHD</p> <p>3) Advise against smoking</p>	

SYSTEM • OUTCOMES	CAUSES HIGHER RISK FACTORS	CLINICAL EVALUATION FREQUENCY OF FOLLOW UP	FURTHER ACTION
<p><b>Gastrointestinal</b></p> <ul style="list-style-type: none"> <li>Nausea, vomiting, diarrhoea, abdominal pain, weight loss</li> <li>Oesophageal stricture → dysphagia</li> <li>Intestinal malabsorption</li> <li>Pancreatic malabsorption</li> </ul>	<ul style="list-style-type: none"> <li>Intestinal infection</li> <li>cGvHD</li> </ul>	<p>Evaluation only needed in presence of overt symptoms</p> <ol style="list-style-type: none"> <li>History and examination – bowel habit, nutritional status, weight</li> <li>High index of suspicion for cGvHD, especially in high-risk patients – look carefully for other features</li> <li>Faecal samples – microbiology (including ova, cysts, parasites), virology, biochemical investigation of malabsorption</li> </ol> <p>At Long Term Follow Up clinic See <i>Gastrointestinal</i></p>	<ol style="list-style-type: none"> <li>Discuss with / refer to Gastroenterologist to consider imaging and / or endoscopy</li> <li>Consider immunosuppressive treatment in chronic gastrointestinal disease associated with cGvHD</li> </ol> <p>See also <i>Gastrointestinal</i></p>
<p><b>Hepatic</b></p> <ul style="list-style-type: none"> <li>Cholestasis, may progress to irreversible liver disease</li> <li>Acute non-infectious hepatitis</li> <li>Sequelae of viral hepatitis</li> <li>Sequelae of hepatic VOD (long term outcome poorly documented in literature but chronic sequelae probably very rare)</li> </ul>	<ul style="list-style-type: none"> <li>Previous GIT surgery</li> <li>RT to field including GIT (including TBI)</li> <li>GvHD (acute or chronic) – usually presents with cholestasis, rarely with acute non-infectious hepatitis</li> <li>Chemotherapy – alkylating agents (especially busulphan), actinomycin D, methotrexate, thiopurines (especially 6TG) (→ VOD)</li> <li>Previous viral hepatitis – usually B or C (both now uncommon in UK)</li> <li>Risk factors for hepatitis B or C, including blood transfusion prior to 1991 (hepatitis C)</li> <li>Pre- / peri-BMT iron overload (eg thalassaemia, aplastic anaemia)</li> </ul>	<p>Routine evaluation needed even in absence of overt symptoms</p> <ol style="list-style-type: none"> <li>History and clinical examination – jaundice, hepatosplenomegaly</li> <li>Measure LFTs</li> <li>High index of suspicion for cGvHD in patients with cholestasis or acute hepatitis – look carefully for other features</li> </ol> <p>See also <i>Hepatic, Recipients of blood products</i></p> <p>At Long Term Follow Up clinic See <i>Hepatic, Recipients of blood products</i></p>	<ol style="list-style-type: none"> <li>Viral detection / serology – hepatitis B, C, other viruses as appropriate</li> <li>Autoantibodies to exclude other causes of acute non-infectious hepatitis</li> <li>Assessment of iron status – ferritin, further investigation as clinically indicated</li> <li>Discuss with / refer to Hepatologist re management of hepatic GvHD (requires immunosuppressive treatment) or other hepatic sequelae</li> </ol> <p>See also <i>Hepatic, Recipients of blood products</i></p>

SYSTEM		CAUSES		CLINICAL EVALUATION		FURTHER ACTION	
• OUTCOMES		HIGHER RISK FACTORS		FREQUENCY OF FOLLOW UP			
<b>Renal</b> <ul style="list-style-type: none"> <li>• Radiation nephritis – chronic glomerular impairment, hypertension, anaemia, haematuria</li> <li>• Glomerular impairment</li> <li>• ?Glomerular hyperfiltration</li> <li>• Proximal tubular impairment</li> <li>• Isolated hypertension</li> <li>• Proteinuria, nephrotic syndrome</li> <li>• Cancer-associated haemolytic uraemic syndrome (C-HUS)</li> </ul>		<ul style="list-style-type: none"> <li>• RT to field including kidneys (including TBI, abdominal, flank)</li> <li>• Chemotherapy – especially platinum agents, ifosfamide, nitrosoureas, ?melphalan</li> <li>• Very intensive chemotherapy conditioning regimens (C-HUS)</li> <li>• Other nephrotoxins – anti-infectives, immunosuppressives</li> </ul>		Routine evaluation needed even in absence of overt symptoms See <i>Renal</i> for detailed investigation schedule In particular, ensure: <ol style="list-style-type: none"> <li>1) Measure BP</li> <li>2) Measure U+E's</li> <li>3) Perform urinalysis for proteinuria and haematuria</li> <li>4) If positive for proteinuria (≥++), measure urine protein : creatinine ratio (UP/UC) in spot urine sample</li> <li>5) High index of suspicion for cGvHD in patients with proteinuria / nephrotic syndrome – look carefully for other features</li> </ol>		<ol style="list-style-type: none"> <li>1) Consider immunosuppressive treatment in nephrotic syndrome associated with cGvHD</li> <li>2) Consider GFR measurement (accurate technique) if high creatinine; discuss with Nephrologist</li> <li>3) Discuss with / refer to Nephrologist if haematuria</li> <li>4) Discuss with / refer to Nephrologist if persistent proteinuria (UP/UC &gt; 100 mg/mmol, or &gt; 50 mg/mmol for ≥ 1 year) to consider treatment with ACE inhibitor ± angiotensin II blocking agent See also <i>Renal</i></li> </ol>	
<b>Lower urinary tract</b> <ul style="list-style-type: none"> <li>• Haemorrhagic cystitis</li> </ul>		<ul style="list-style-type: none"> <li>• ARF during BMT</li> <li>• Hepatic VOD during BMT</li> <li>• Previous nephrectomy</li> <li>• ?Young age (ifosfamide)</li> <li>• cGvHD – associated with proteinuria / nephrotic syndrome</li> </ul>		At Long Term Follow Up clinic See also <i>Renal</i> , but more specifically: <ol style="list-style-type: none"> <li>1) Measure BP at least annually</li> <li>2) Measure U+E's annually</li> </ol>		See <i>Lower Urinary Tract</i>	
		<ul style="list-style-type: none"> <li>• RT to field including lower urinary tract (including TBI, abdominal, pelvic, spinal)</li> <li>• Chemotherapy – cyclophosphamide, ifosfamide,</li> <li>• Viral infection – CMV, adenovirus, papovavirus</li> <li>• cGvHD - ? due to association with immunosuppression and viral infection</li> <li>• Previous lower urinary tract surgery</li> </ul>		Routine evaluation needed even in absence of overt symptoms See <i>Lower Urinary Tract</i> In particular, ensure: <ol style="list-style-type: none"> <li>1) Perform urinalysis for haematuria</li> </ol> At Long Term Follow Up clinic See <i>Lower Urinary Tract</i>			

SYSTEM • OUTCOMES	CAUSES HIGHER RISK FACTORS	CLINICAL EVALUATION FREQUENCY OF FOLLOW UP	FURTHER ACTION
<p><b>Musculoskeletal</b></p> <ul style="list-style-type: none"> <li>Sclerodermatous joint contractures</li> </ul> <p><u>Muscular</u></p> <ul style="list-style-type: none"> <li>Polymyositis</li> <li>Weakness</li> </ul> <p><u>Skeletal</u></p> <ul style="list-style-type: none"> <li>Avascular necrosis (AVN)</li> <li>Osteochondroma (OC)</li> <li>Reduced BMD</li> <li>Slipped epiphysis</li> <li>Scoliosis</li> </ul>	<p><u>Muscular</u> / <u>musculoskeletal</u></p> <ul style="list-style-type: none"> <li>cGvHD</li> </ul> <p><u>Skeletal</u></p> <ul style="list-style-type: none"> <li>RT to field including affected bone (AVN, OC) (including TBI)</li> <li>Cranial RT (→ GH deficiency)</li> <li>Chemotherapy, especially methotrexate (reduced BMD)</li> <li>Steroids (AVN, reduced BMD)</li> <li>Older age (AVN rare &lt;10 years age)</li> <li>Male gender (AVN)</li> <li>Endocrinopathy (GH deficiency, hypogonadism both → reduced BMD; GH deficiency also → muscle weakness)</li> </ul>	<p>Routine evaluation needed even in absence of overt symptoms</p> <ol style="list-style-type: none"> <li>History and examination – diet, exercise, fractures, joint movements and pain, muscle weakness, back pain, gait</li> <li>High index of suspicion for cGvHD in patients with sclerodermatous joint contractures – look carefully for other features</li> <li>Consider measurement of BMD by DEXA scan, especially in patients treated for GH deficiency or hypogonadism</li> </ol> <p>See also <i>Bone Density</i></p> <p>At Long Term Follow Up clinic</p> <ol style="list-style-type: none"> <li>Ideally perform DEXA scan 1 year post-BMT, then at regular intervals especially in patients treated for GH deficiency or hypogonadism</li> </ol> <p><b>NB</b> Need to interpret DEXA results using size-related reference ranges</p>	<ol style="list-style-type: none"> <li>Review immunosuppressive treatment in musculoskeletal disease associated with cGvHD</li> <li>Encourage calcium-rich diet and exercise, discuss with / refer to Specialist in Bone Disease in patients with reduced BMD</li> <li>Perform MRI if suspicion of AVN</li> <li>Discuss with / refer to Orthopaedic Surgeon in patients with AVN, OC, slipped epiphysis or scoliosis</li> </ol>
<p><b>Skin</b></p> <ul style="list-style-type: none"> <li>Wide range of features of cGvHD – erythema, hypo / hyperpigmentation, vitiligo, poikiloderma, lichenoid and / or sclerodermatous lesions</li> <li>Alopecia</li> <li>Benign pigmented naevi</li> <li>Tumours – melanoma, squamous cell carcinoma (SCC)</li> </ul>	<ul style="list-style-type: none"> <li>cGvHD</li> <li>RT (skin in field)</li> <li>Chemotherapy (all skin)</li> <li>cGvHD – associated with skin SCC</li> <li>Fanconi anaemia</li> </ul>	<p>Routine evaluation needed even in absence of overt symptoms</p> <ol style="list-style-type: none"> <li>History and examination – suspicious skin lesions</li> <li>Photography of lesions where appropriate</li> <li>High index of suspicion for cGvHD in patients with suspicious skin lesions – look carefully for other features</li> </ol> <p>See also <i>Skin</i></p> <p>At Long Term Follow Up clinic</p>	<ol style="list-style-type: none"> <li>Refer to Dermatologist for examination of suspicious skin lesions – consider biopsy / excision biopsy as appropriate</li> <li>Review immunosuppressive treatment in skin disease associated with cGvHD</li> <li>Encourage avoidance of excessive sunlight / UV light</li> </ol> <p>See also <i>Skin</i></p>

## NOTES

- a) Late adverse effects in patients who have undergone BMT may be due to treatment received before, during or after the BMT.
- b) The shaded portion (“sub-row”) of this column in each section (eg Quality of Life) refers specifically to Higher risk factors.
- c) Cross references denoted in italics refer to the other sections of this Practice Statement.
- d) The statement “At Long Term Follow Up clinic” assumes that this will enable regular evaluation at yearly (or occasionally two-yearly) intervals, unless there are specific indications for more frequent assessment (as discussed in the introductory comments to this Appendix, paragraph 5).
- e) The shaded portion (“sub-row”) of this column in each section (eg Quality of Life) refers specifically to Frequency of follow up.
- f) Discussion with / referral to other specialists – although not explicitly stated, it is expected that paediatric specialists will be consulted unless patient age (adolescent or young adult) or local circumstances or expertise dictate otherwise.

## ABBREVIATIONS

6TG	6-thioguanine
AML	acute myeloid leukaemia
ARF	acute renal failure
AVN	avascular necrosis
BMD	bone mineral density
BO	bronchiolitis obliterans
BOOP	bronchiolitis obliterans with organising pneumonia
cGvHD	chronic graft-versus-host disease
C-HUS	cancer-associated haemolytic uraemic syndrome
CMV	cytomegalovirus
CVA	cerebrovascular accident
CXR	chest X-ray
FA	Fanconi anaemia
FBC	full blood count
GIT	gastrointestinal tract
GH	growth hormone
HbA <sub>1c</sub>	glycosylated haemoglobin
IP	interstitial pneumonia
LFTs	liver function tests
MDS	myelodysplasia
OC	osteochondroma
RT	radiotherapy
SCC	squamous cell carcinoma
T <sub>4</sub>	thyroxine
TBI	total body irradiation
TFTs	thyroid function tests
TLI	total lymphoid irradiation
TSH	thyroid stimulating hormone
U+Es	urea, creatinine and electrolytes

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**TABLE II**  
**CHECK LIST FOR HISTORY, EXAMINATION, SURVEILLANCE INVESTIGATION**

Consider the following regularly\* at Long Term Follow Up clinic  
 Additional investigations may be appropriate if abnormal symptoms / signs

**History**

School / employment  
 Quality of life  
 Growth  
 Nutrition, weight gain  
 Pubertal development } at appropriate  
 Fertility issues } age / time  
 Joint pain (especially hip, knee)  
 Vision  
 Dental health  
 Compliance with medications eg anti-infective prophylaxis  
 Immunisation up to date (as appropriate)  
 Health education as appropriate, including smoking, sunlight, breast examination

**Examination**

Height (including sitting height if possible), } 3-6 monthly until  
 weight, calculate height velocity } puberty and  
 Pubertal assessment (Tanner stage) } growth completed  
 Skin (cGvHD, naevi, suspicious lesions) – consider clinical photography  
 Thyroid palpation  
 CNS examination  
 Ophthalmoscopy (cataracts)  
 Blood pressure

**NB** Wide variety of symptoms / signs of cGvHD

**Investigations**

FBC  
 Biochemical profile (incl U+Es, LFTs, albumin, protein, calcium, phosphate, magnesium)  
 Thyroid function tests (T<sub>4</sub>, TSH)  
 LH, FSH, oestradiol<sup>†</sup> / testosterone } after 10 years  
 Inhibin B (if available) } age  
 Fasting glucose and lipids  
 HbA<sub>1c</sub>  
 Immunoglobulins, lymphocyte subsets (only if clinical concern about delayed or poor immune reconstitution)  
 IGF-1 } in TBI recipients if concern  
 Bone age } about growth  
 Urinalysis (haematuria, proteinuria, glycosuria)  
 ?Urine cytology  
 Echocardiogram (annually if abnormal, 3-5 yearly if normal)  
 Pulmonary function tests (annually if abnormal or if new symptoms, 3-5 yearly if normal and no symptoms)  
 Chest X-ray (if symptomatic or PFTs severely abnormal)  
 ?Bone mineral density by DEXA (especially in patients treated for GH deficiency or hypogonadism)

\* eg yearly (see introductory notes above) except where indicated otherwise – see Table I for further details

† not helpful if on hormone replacement treatment