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# Late effects among survivors of acute lymphoblastic leukemia: the ALL-STAR study protocol.

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# Late effects among survivors of acute lymphoblastic leukemia: the ALL-STAR study protocol.

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**ABSTRACT**

**Introduction:** More than 90% of patients diagnosed with childhood acute lymphoblastic leukemia (ALL) today will survive. However, half of survivors are expected to experience therapy-related chronic or late occurring adverse effects, reducing quality of life. Insight into underlying risk trajectories is warranted. The aim of this study is to establish a Nordic, national childhood ALL survivor cohort, to be investigated for the total somatic and psychosocial treatment-related burden as well as associated risk factors, allowing subsequent linkage to nation-wide public health registers.

**Methods and analysis:** This population-based observational cohort study includes clinical follow-up of a childhood ALL survivor cohort (N=475), treated according to a common Nordic ALL protocol during 2008-2018 in Denmark. The study includes matched controls. Primary endpoints are the cumulative incidence and cumulative burden of 197 health conditions, assessed through self- and proxy-report questionnaires, medical chart validation, and clinical examinations. Secondary endpoints include organ-specific outcome including cardiovascular and pulmonary function, physical performance, neuropathy, metabolic disturbances, hepatic and pancreatic function, bone health, oral and dental health, kidney function, puberty and fertility, fatigue, and psychosocial outcome. Therapy exposure, acute toxicities and host genome variants are explored as risk factors.

**Ethics and dissemination:** The study is approved by the Regional Ethics Committee for the Capital Region in Denmark (H-18035090/H-20006359) and by the Danish Data Protection Agency (VD-2018-519). Results will be published in peer-reviewed journals and are expected to guide interventions that will ameliorate the burden of therapy without compromising chance of cure.



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**STRENGTHS AND LIMITATIONS OF THIS STUDY**

- The ALL-STAR cohort is the first population-based, uniformly treated, Nordic childhood and young adult ALL survivor cohort to be systematically evaluated for treatment-related organ-wide morbidity and psychosocial impact, thus supplementing National public demographic, socio-economic and health registries.
- Strengths of this study include the population-based, homogenous survivor cohort, use of matched controls, systematic assessment of outcome using both survivor reports and clinical investigations, and a transparent and precise definition of outcomes, which has been aligned with previous reporting systems.
- Analysis of results includes the cumulative burden which includes recurrent events, thereby describing the total disease burden more comprehensively than traditional measures such as cumulative incidence.
- A follow-up of 3.5-14 years at time of evaluation means that the full burden of previous ALL and therapy will not be captured, however, the infrastructure created will facilitate longitudinal studies.
- Results will supplement existing data describing the treatment-related burden and the underlying possible genetic, biological, physical and psychosocial mechanisms, while providing novel insight into differences related to specific therapy regimens, health cultures and health care systems.

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## 1. INTRODUCTION

Five-year overall survival rates for childhood acute lymphoblastic leukemia (ALL) has climbed from less than 10% to above 90% during the last seven decades as a result of chemotherapy intensification, refined risk stratification, and improved supportive care.[1–3] However, cure comes at a cost.[4] All patients experience acute but transient toxicities during therapy (e.g. infections, mucositis and peripheral neuropathy), and half of patients are burdened by at least one severe, potentially life-threatening organ toxicity such as acute pancreatitis, thromboembolism, or severe neurotoxicity.[5–8] Acute organ damage resulting from leukemia and/or therapy may persist (e.g. insulin dependent diabetes[9]) or emerge (e.g. osteonecrosis[10]) several years into survival as late effects. The 30-year old survivor will have experienced an average of 5.4 health conditions, and half of survivors face at least one chronic health condition 20 years from ALL diagnosis, both measures significantly exceeding those among siblings and community controls.[11,12] This disproportion in morbidity rate seems to amplify with increasing age.[12] Certain therapeutic exposures have been reduced over time (e.g. reduction in cardiotoxic anthracycline exposure and limited use of cranial irradiation in first-line therapy protocols),[13,14] which has decreased risk of early mortality and lowered the prevalence of treatment-related cancers, severe cognitive deficits, hypothalamic-pituitary dysfunction, and immunological disease.[12,14] However, the number of health conditions per individual survivor is still double that in controls and now mainly include endocrine system disorders, musculoskeletal-, neurological-, and cardiovascular conditions,[12] maintaining risk of impaired physical, cognitive, and emotional function, socioeconomic achievements, and health-related quality of life.[11,15–18] Therapy exposure and genetic susceptibility are considered the two major risk factors predicting late morbidity.[19] Risk of specific late effects are associated with cumulative chemotherapy exposures,[20–29] but no safe lower doses have been established. Specific genetic variants have been linked with survivor obesity, reduced bone mineral density, cardiotoxicity, skeletal muscle dysfunction, and neurocognitive dysfunction,[30–33] however, clinical recommendations await harmonization of outcomes, larger sample sizes, and replication in independent cohorts.[30] To date, many late effects studies are observational and focus on one or few organ systems, cross-sectional in design, or emerge from single centers with resulting risk of selection bias and limited sample power. A few very large (>10,000 patients), multi-institutional childhood cancer survivor cohort studies exist, such as the US Childhood Cancer Survivor Study,[34] the Nordic Adult Life after Childhood Cancer in Scandinavia study,[35] and the British Childhood Cancer Survivor Study[36]. Most studies emerging from these cohorts rely on self-reported and register-based data, while few include



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systematic clinical data, none of which include Nordic survivors.[37]

During the 10-year period 2008-2018, patients diagnosed with Philadelphia-chromosome negative ALL at age 1–45 years in the Nordic and Baltic countries, have been treated according to the Nordic Society of Pediatric Hematology and Oncology (NOPHO) ALL2008 protocol described elsewhere.[3,5,38] Two thirds of this cohort were below 18 years of age at diagnosis. The aim of the Acute Lymphoblastic Survivor Toxicity And Rehabilitation (ALL-STAR) study is to establish a national, Danish NOPHO ALL2008 survivor cohort, to be assessed for the total somatic and psychosocial treatment-related burden, using both self-report and systematic clinical data that will supplement data from the Danish Nation-wide public demographic, socio-economic and health registries.[39]

## 2. METHODS

### Study aims

*Primary aim*

To quantify the burden of health conditions occurring during the first decade of survivorship among survivors of childhood and young adult ALL.

*Secondary aims*

To describe, in detail, organ-specific health among survivors as compared to matched controls and normative data; and to investigate host genome variants, therapy exposure, and acute toxicities as risk factors for organ-specific late effects and for the overall cumulative burden. Furthermore, to develop a follow-up program that can subsequently be expanded to the Nordic/Baltic region for patients treated according to the same protocol.

An overarching structural aim of the ALL-STAR project is to establish a platform for life-long follow-up in this survivor cohort, facilitating longitudinal studies and linkage to Nation-wide public, socio-economic and health registries. This present protocol describes the initial phase of the project.

### Study design

The ALL-STAR study is a national, Danish, population-based, observational cohort study, including prospective clinical follow-up in a retrospective childhood and young adult ALL survivor cohort.



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**Participants**

*Study population*

All survivors treated in Denmark according to the NOPHO ALL2008 protocol and minimum one year from therapy cessation (3.5 years from ALL diagnosis) are eligible. This corresponds to all patients (N=475) aged 1–45 years at diagnosis with Ph$^-$ B-cell precursor or T-cell ALL, diagnosed between July 2008 and October 2018 (the complete NOPHO All2008 protocol period). A control group consisting of age- and sex-matched individuals (1:1) is recruited for the study. First degree relatives to survivors and individuals with previous or ongoing cancer, previous or ongoing chemotherapy and/or previous or ongoing radiation therapy are excluded as controls. Study recruitment opened in February 2019 and will terminate in September 2022, allowing for the entire survivor cohort to meet inclusion criteria.

*Recruitment*

Eligible survivors are identified through the NOPHO ALL2008 registry. Contact information is obtained through medical charts and provided by treating physicians to the research team. Written information material is sent to survivors aged ≥18, to survivors and parents if aged 15–17.9, and to parents if aged <15. Contact is obtained through subsequent phone calls. All survivors and/or families are invited to an on-site meeting for further information before consent. Controls are recruited via participating survivors (or parents) who appoint and invite friends or relatives to participate. Potential controls (or parents) contact the research team, with subsequent written and oral information provided as described for survivors, before possible consent.

**Endpoints**

*Primary endpoints and hypothesis*

The two primary endpoints are cumulative incidence and cumulative burden of 197 health conditions presented in Table 1.



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**Table 1. Health conditions investigated in the ALL-STAR study**

| AUDITORY-HEARING | GASTROINTESTINAL | INFECTIONS | NEUROLOGIC | PULMONARY |
|---|---|---|---|---|
| Cholesteatoma | Bowel perforation | Bronchial/lung infection C/R | Autonomic dysfunction | Asthma |
| Hearing loss | Celiac disease | Endocarditis | Cavernoma | COPD |
| Tinnitus | Constipation | Gastrointestinal infection | Cerebellar dysfunction | Epistaxis, chronic/recurrent |
| Vertigo | Dysphagia | Genitourinary infection | Cerebral necrosis | Obstructive sleep apnea |
| | Enterocolitis | Hepatitis B, chronic | Cerebrovascular accident | Obstructive ventilatory defect |
| **CARDIOVASCULAR** | Esophageal varices | Hepatitis C, chronic | Cerebrovascular disease | Pleural space disorders |
| Aortic root aneurysm | Esophagitis | HIV infection | Cranial nerve disorder | Pneumonitis |
| Arteriovenous malformation | Fecal incontinence | Lymphatic infection | Dysarthria | Pulmonary diffusion defect |
| Atrioventricular heart block | Gastritis/duodenitis | Meningoencephalitis | Generalized muscle weakness | Pulmonary embolism |
| Bradycardia, sinus | GERD | Osteomyelitis | Headaches, chronic/ recurrent | Respiratory tract hemorrhage |
| Cardiopulm. fitness, reduced | Gastrointestinal fistulas | Otitis media, C/R | Hydrocephalus | Restrictive ventilatory defect |
| Conduction abnormalities | Gastrointestinal hemorrhage | Pelvic inflammatory disease | Hydrosyringomyelia | Tracheal aspiration |
| Congestive heart failure | Gastrointestinal necrosis | Pharyngitis/tonsillitis, C/R | Intracranial hemorrhage | Tracheal stenosis |
| Coronary artery disease | Gastrointestinal obstruction | Sinusitis, C/R | Movement disorders | |
| Cor pulmonale | Gastrointestinal strictures | Soft tissue infection | Multiple sclerosis | **PSYCHIATRIC** |
| Dysrhythmia | Gastrointestinal ulcer | | Narcolepsy | Anxiety |
| Heart valve disorder | Gastroparesis syndrome | **MUSCULOSKELETAL** | Nerve root disorder | Depression |
| High total cholesterol | Malabsorption syndrome | Amputation | Neurogenic bladder | Other psychiatric disorders |
| Hypertension | Pancreatic insufficiency | Arthralgia | Neurogenic bowel | |
| Hypertriglyceridemia | Pancreatitis | Arthritis | Neuromuscular disorders | **RENAL / URINARY** |
| LV systolic dysfunction | Proctitis | Bone mineral density deficit | Paralytic disorder | Acute kidney injury |
| Pericarditis | | Hernia | Peripheral motor neuropathy | Chronic hematuria |
| Prolonged (QTc) interval | **HEPATOBILIARY** | Intervertebral disc disorder | Peripheral sensory neuropathy | Chronic kidney disease |
| Pulmonary hypertension | Cholecystitis/Cholelithiasis | Kyphosis | Pseudomeningocele | Incontinence |
| Raynaud phenomenon | Fibrosis/Cirrhosis | Limb length discrepancy | Pseudotumor cerebri | Obstructive uropathy |
| RV systolic dysfunction | Hepatic failure | Osteonecrosis | Seizures | Urinary bladder dysfunction |
| Tachycardia, sinus | Hepatopathy | Palatal defects, acquired | | Urinary tract calculi |
| Thromboembolic event | Portal hypertension | Scoliosis | **OCULAR/VISUAL** | Vesicoureteral reflux, acquired |
| Vascular disease | Veno-occlusive disease | Skeletal spine disorder | Cataract | |
| | | Slipped capital femoral epiphysis | Diplopia | **REPRODUCTIVE / GENITAL** |
| **ENDOCRINE** | **HEMATOLOGIC** | | Dry eye syndrome | Abnormal sperm concentration |
| Abnormal glucose metabolism | Anemia | **ORAL / DENTAL** | Eyelid function disorder | Cervical dysplasia |
| Adrenal insufficiency | Coagulopathy | Dental caries | Glaucoma | Dysfunctional uterine bleeding |
| Adult GH deficiency | Iron overload | Dental erosion | Ocular disease, noninfectious | Endometriosis |
| Childhood GH deficiency | Neutropenia | Gingivitis | Ocular surface disease | Erectile dysfunction |
| Diabetes insipidus | Polycythemia | Periodontitis | Photophobia | Genitourinary adhesions |
| GH excess | Thrombocytopenia | Sialadenitis, acute | Phthisis bulbi | Hypogonadism, central |
| Hyperparathyroidism | Thrombocytosis | Sialadenitis, chronic | Retinal detachment | Leydig cell insufficiency |
| Hyperprolactinemia | | Salivary gland dysfunction | Retinopathy | Polycystic ovarian syndrome |
| Hyperthyroidism | **IMMUNOLOGIC** | TMJ disorder | Strabismus | Precocious puberty |
| Hypoparathyroidism | Autoimmune disorders | Dental maldevelopment | Visual acuity, reduced (OD) | Primary ovarian failure |
| Hypothyroidism | Graft-versus-host disease | | Visual acuity, reduced (OS) | Prostatic hypertrophy, benign |
| Overweight/Obesity | Immunodeficiency | **NEOPLASMS** | Visual field deficit | Vaginal fistula |
| Sarcopenic obesity | | Benign neoplasms | | Vaginal stenosis |
| SIADH | | Malignant neoplasms | | |
| Underweight | | | | |

Abbreviations: Cardiopulm. Fitness, red. = cardiopulmonary fitness, reduced; COPD = Chronic obstructive pulmonary disease; CR = chronic/recurrent, GERD = gastroesophageal reflux disease; GH = growth hormone; LV = left ventricle; RV = right ventricle; SIADH = syndrome of inappropriate antidiuretic hormone secretion; TMJ = temporomandibular joint; QTc = corrected QT interval



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We hypothesize that the cumulative incidence and cumulative burden are significantly higher among survivors of childhood and young adult ALL already during the first decade of survival, when compared with sex- and age- matched controls and normative data.

The measure of cumulative burden considers occurrence of multiple health conditions and recurrent events, thereby encompassing the total disease burden more comprehensively than cumulative incidence which includes only first occurrence of an event.[40,41] The 197 conditions investigated in the ALL-STAR study are defined and graded according to the St Jude Children's Research Hospital modification of the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE; version 4.03),[42] developed to optimize characterization of long-term and late-onset health conditions among childhood cancer survivors.[43] Ten additional health conditions (generalized muscle weakness, reduced cardiopulmonary fitness, sarcopenic obesity, and seven oral/dental conditions) have been added. Definitions and grading criteria for all conditions are provided in Supplementary Table 1.

*Secondary endpoints*

Secondary endpoints include 1) organ-specific outcome including metabolic syndrome and body composition, hepatic function, pancreatic function, bone health, cardiac function, pulmonary function, peripheral- and autonomic neuropathy, physical performance, kidney function, pubertal timing, fertility, oral and dental health and 2) psychosocial outcome including emotional distress, fatigue, and health-related quality of life.

An overview of the ALL-STAR study is provided in Figure 1.

**Data collection**

Data are collected through questionnaires and clinical evaluations. An overview of ALL-STAR source data used for evaluation of the 197 health conditions is provided in Supplementary Table 1.

Questionnaire data

An electronic questionnaire is sent to participants prior to clinical examinations. The questionnaire is adjusted according to self-report (age ≥ 15 years), proxy-report (age < 18), age, sex, and status as survivor or control. Items include demographics, use of health care services, medicine and nutritional supplements, medical history (including age at the onset of a confirmed condition), pubertal status and fertility, familiar dispositions, health behavior, mental



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health, quality of life, and socioeconomic status. An overview of questionnaire versions and content is provided in Supplementary Table 2.

Clinical data

All clinical examinations are performed at either Copenhagen University Hospital or Aarhus University Hospital, as requested by the participant. Examinations are performed during 10 hours in a single day. The examination program and description of clinical investigators are provided in Supplementary Table 3.

*Evaluation of metabolic syndrome and body composition*

Endpoints include metabolic syndrome (MetS), insulin sensitivity, lipid profile, abdominal circumference, body mass index (BMI) for adults and BMI standard deviation scores for children, based on national reference material,[44,45] lean body mass and fat mass. Adult MetS is defined according to the *National Cholesterol Education Program Adult Treatment Panel* criteria,[46] and includes central obesity, dyslipidemia, hypertension, and elevated fasting glucose. Pediatric MetS is defined using the same measures.[47] Questionnaire items include metabolic disease and family disposition, prescription medicine, nutritional supplements, and lifestyle (diet, level of physical activity and sedentary behavior). Clinical investigations include anthropometrics (weight, height and abdominal circumference) and blood pressure (described in cardiovascular section). Fasting blood samples include glucose, glycated hemoglobin, insulin, pro-insulin c-peptide, total cholesterol, high density lipoprotein cholesterol, low-density lipoprotein cholesterol, very low-density lipoprotein cholesterol, triglycerides, glucagon, and leptin. Homeostatic Model Assessment for Insulin resistance score is calculated as fasting plasma glucose (mmol/L) x fasting plasma insulin (microU/L)/22.5.[48] Body composition (fat and lean body mass and android/gynoid fat distribution) is assessed with dual-energy X-ray absorptiometry (DXA) (Lunar Prodigy, GE Healthcare, WI, USA; or Hologic Horizon A, Hologic, Marlborough, MA, USA), and is adjusted for sex and pubertal stage.

*Evaluation of hepatic function and gallbladder*

Endpoints include signs of hepatocellular damage, impaired liver synthesis, iron overload, hepatic fibrosis, portal hypertension, and gall bladder disease (cholestasis, cholangitis, cholelithiasis). Questionnaire items include symptoms of hepatic disease (fatigue, abdominal pain, nausea, jaundice, discolored urine, itchy skin), hepatic diagnoses, alcohol consumption and use of prescription medicine. Fasting blood samples include alanine transaminase, aspartate



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transaminase, alkaline phosphatase, gamma-glutamyl transferase, bilirubin, lactate dehydrogenase, prothrombin time, international normalized ratio, albumin, ferritin, transferrin saturation, alfa-1 antitrypsin, platelets and immunoglobulins. Serum is stored for evaluation of viral antibodies (Hepatitis A, B, C, Cytomegalovirus and Epstein-Barr virus) in case of elevated transaminases. Hepatic ultrasound is performed using a convex, abdominal probe (C1-5, GE Logiq E9 or E10, GE Healthcare, Chicago, USA). The liver, gallbladder, gall ducts, liver artery and spleen are evaluated for appearance and size. Portal vein flow is measured using Doppler. Ultrasound 2D shear wave elastography is performed on the right liver lobe for evaluation of parenchymal stiffness and fibrosis.[49]

*Evaluation of pancreatic function*

Endpoints include pancreatic disease, endocrine and exocrine function, and morphological appearance. Questionnaire items include pancreatic symptoms and disease, diet and alcohol consumption. Fasting blood samples include pancreatic amylase, lipase, glucose, glycosylated hemoglobin, insulin, and proinsulin c-peptide. Fecal elastase-1 is evaluated in survivors only. Pancreatic ultrasound is performed using a convex, abdominal probe (C1-5, GE Logiq E9 or E10, GE Healthcare, Chicago, USA) for anterior-posterior measurement of caput and corpus, and for evaluation of morphological changes (tumor, inflammation, edema, pseudocysts, and ductal ectasia).

*Evaluation of bone mineral density*

Endpoints include bone mineral density (BMD), bone fractures, and biomarkers of bone metabolism. Questionnaire items include bone- and joint symptoms, history of fractures and low BMD, age of menarche, hormone supplements, calcium and vitamin D intake, and family history of bone disease. Biomarkers include ionized calcium, phosphate, alkaline phosphatase, parathyroid hormone, and 25-OH-vitamin D. Bone mineral content, bone area, and BMD is determined by DXA (Lunar Prodigy, GE Healthcare, WI, USA; or Hologic Horizon A, Hologic, Marlborough, MA, USA) total body, lumbar spine (L1-L4), and dual-femur scans. Adult bone mineral values are analyzed as age- and sex-specific standard deviations and expressed as z- and T-scores, based on unpublished USA reference material. Pediatric bone mineral values are analyzed as age- and sex-specific standard deviations and expressed as z-scores, based on unpublished German reference material. All pediatric bone mineral values are corrected for height.

*Evaluation of cardiovascular function*

Endpoints include left and right ventricular systolic and diastolic dysfunction, ventricular volumes and left ventricular mass, myocardial fibrosis, myocardial iron deposits, atrial thrombosis, conduction abnormalities and hypertension.



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Questionnaire items include cardiovascular symptoms, diagnoses, prescription medicine, and familiar disposition to cardiovascular disease. Automated oscillometric blood pressure is measured in all, and manual auscultatory systolic blood pressure is measured in children (< 18 years). Cardiac biomarkers include N-terminal pro b-type natriuretic peptide and troponin-T. Cardiac electrical activity is assessed with a 12-lead electrocardiogram (ECG). Imaging includes speckle tracking echocardiography and cardiac magnetic resonance imaging (MRI). Echocardiography is performed using a Vivid E95 ultrasound scanner (GE Healthcare Vingmed Ultrasound AS, Horten, Norway) to obtain measurements of left ventricular output and volumes, as well as global longitudinal systolic strain. An intravenous contrast agent (SonoVue®) is used to improve imaging.[50] Cardiac MRI is performed using a whole body 1.5T scanner for assessment of left ventricular systolic function, volumes, and mass. Multiparametric characterization including T1, T2, T2*and mapping is performed for visualization of possible myocardial edema and fibrosis, and to evaluate myocardial iron content.[51,52] Intravenous gadolinium-containing contrast (0,15 mmol/kg Gadovist®) is used for assessment of extracellular volume fraction in survivors (not controls).

*Evaluation of pulmonary function*

Endpoints include function of conductive and acinar airways, resistance of airways, alveolar volumes, alveolar membrane diffusion, lung clearance index, capillary volume, total diffusion capacity, spirometric volumes and flows, and reversibility. Questionnaire items include respiratory symptoms, pulmonary diagnoses, smoking and use of prescription medicine. Prebronchodilator and postbronchodilator spirometry is performed using a Jaeger MasterScreen Bodybox and Jaeger Vyntus Spiro (CareFusion, Hochberg, DE; Vyaire Medical, Bayern, DE) for measurement of forced expiratory volume during the first second, forced vital capacity (FVC), and forced expiratory flow between 25% and 75% of FVC. Impulse oscillometry including reversibility test is performed at University Hospital of Aarhus using a Jaeger MasterSceen Bodybox and Jaeger Vyntus IOS system (CareFusion, Hochberg, DE; Vyaire Medical, Bayern, DE) to evaluate lung volumes, resistance and elasticity of the lung. Nitrogen multiple breath washout is performed using an Ecomedics Exhalyzer D, N2 and SF6 option (Ecomedics, Dürnten, CH) to assess Lung Clearance Index including indexes of acinar and conductive airways ventilation heterogeneity. Single breath diffusion capacity for carbon monoxide and nitrogen oxide, corrected for hemoglobin, is performed using a Jaeger Vyntus Body (CareFusion, Hochberg, DE) for real time Single Breath diffusion to evaluate diffusion membrane capacity and



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pulmonary capillary volume. All pulmonary measures are compared with normative data[53–58] and with data from the matched controls.

*Evaluation of peripheral and autonomic neuropathy*

Endpoints include sensory-, motor-, and autonomic nerve dysfunction. Peripheral neuropathy is assessed according to recommendations from *American Academy of Neurology, the American Association of Electrodiagnostic Medicine* and *American Academy of Physical Medicine and Rehabilitation,*[59] and using the Total Neuropathy Score, which includes self-report of sensory, motor and autonomic symptoms, pin sensibility, vibration sensibility (quantitative threshold using Vibrameter® type IV (SOMEDIC Electronics, Solna, Sweden) and Biothesiometer® model PVD-LP (Bio Medical Instruments company, Ohio, USA)), muscle strength (Medical Research Council 5-grade score), deep tendon reflexes and amplitude of sural and peroneal nerves.[60] Abnormal values corresponding to quantitative vibration threshold are calculated as percentages relative to the upper limit of normal values based on data from matched ALL-STAR controls and previously published normative data.[61–63] Electroneurography is performed using standard surface recording techniques (Neuroline 715, Ambu®). A G3 Keypoint platform (DanTec, Natus, USA) is used for amplification, filtration and storing of signals (motor: 2Hz-10kHz; sensory: 20Hz-10kHz). Electroneurography includes unilateral evaluation of Sensory Nerve Action Potential from the sural nerve, compound Motor Action Potential from the peroneal nerve, the distal motor latency in the peroneal nerve and both sensory and motor nerve conduction velocities. Recorded values are compared with ALL-STAR controls values and with unpublished national, Danish age- and gender-specific reference values, and reported as standard deviations from the expected mean (z-scores). Autonomic neuropathy is evaluated with the validated 31-item composite autonomic symptom questionnaire, COMPASS 31[64,65], which assesses orthostatic intolerance, vasomotor, secretomotor, gastrointestinal, bladder and pupillomotor function. Objective evaluation of autonomic dysfunction is performed by analysis of heart rate variability (HRV) obtained from a 21-minutes Holter recording (13 minutes reclined resting period followed by shift to standing position with continued ECG recording for eight minutes). The RR-interval dataset derived from the ECG segments is analyzed for heartrate and HRV. Analysis of HRV is performed in both the time and frequency domain and changes elicited by the standing position is calculated.

*Evaluation of physical performance*

Endpoints include cardiorespiratory fitness, level of physical activity, physical function and muscle strength.



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Questionnaire items include levels of sedentary behavior and of physical activity, which is objectified with a 7-day continuous accelerometer measurement (ActiGraph™ model GT3X+, ActiGraph LLC, Pensacola FL, USA). Cardiorespiratory fitness is evaluated using an electronically braked cycle ergometer (Lode Corival Pediatric or Monark Ergomedic 839 E) following a modified Godfrey protocol.[66,67] Ventilation and gas exchange data are determined breath-by-breath (INNOCOR ergo-spirometry-system, INNO00010, Innovision, DK-5260 Odense, Denmark or Jaeger Master Screen® Vyntus CPX and JLAB Software Package™). Peak oxygen uptake ($VO_2$peak) is defined as the highest mean over 60 seconds. Results are reported as standard deviations from the expected mean (z-scores), derived from the age- and sex-matched ALL-STAR controls. Muscle strength is evaluated as isometric muscle strength (knee extensor, upper body (Gym 2000) with a Strain gauge (US2A100 kg, Holtinger, Germany) and custom-made amplifier), and handgrip strength (Saehan hand dynamometer, Glanford Electronics, Scunthorpe). Dynamic muscle strength is evaluated by the counter movement jump test (FP4, HUR-Labs Oy, Tampere, Finland) and physical function (Sit-to-stand 30s and 60s[68], Timed-Up-and-Go[69]).

*Evaluation of kidney function*

Endpoints include kidney function and kidney size. Questionnaire items include urinary tract symptoms and disease and use of prescription medicine. Fasting blood-samples include creatinine, urea, cystatin-c, sodium, potassium, phosphate, albumin, ionized calcium, and parathyroid hormone. Estimated glomerular filtration rate is evaluated using creatinine in adults,[70] and using creatinine, urea and cystatin-C in children[71]. Proteinuria is determined by the albumin-creatinine ratio in a morning urine specimen. A spot urine dip stick test is performed to evaluate hematuria and urine pH. Kidney size is evaluated by ultrasonography (convex, abdominal probe (C1-5), GE Logiq E9 or E10, GE Healthcare, Chicago, USA) as longitudinal anterior-posterior length, width and cross-sectional ap-length, and abnormal appearance (e.g. hydronephrosis, cysts or tumors) is registered. Kidney size is related to body weight, height and lean mass.

*Evaluation of pubertal status and gonadal function*

Pubertal stage is evaluated in all participants aged > 8 years at time of evaluation. Endpoints include age at menarche/spermarche, pubertal stage, and levels of reproductive hormones. Questionnaire items include age at menarche and use of contraception for females, age at spermarche for males, and hormonal substitution. Pubertal stage is evaluated according to Tanner[72] in combination with testicular volume for males, estimated by comparative



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palpation using a Prader orchidometer[73]. Results are compared with Danish puberty normograms.[74,75] Measurements of serum follicle stimulating hormone, luteinizing hormone, estradiol, testosterone, insulin-like peptide 3, inhibin B, anti-müllerian hormone, and sex hormone binding globulin are performed and levels are compared with unpublished sex-, and age matched national reference material as well as with ALL-STAR controls.

*Evaluation of fertility*

Fertility is evaluated in all participants aged ≥ 18 years. Endpoints include impaired fertility (defined as previously diagnosed impaired fertility or infertility and/or use of assisted reproductive technology), number and health of offspring. Questionnaire data include items regarding health behavior, previous relationship/marital status, attempts to conceive, menopause, results from fertility investigations, natural conceptions, use of assisted reproductive technology, pregnancies, miscarriages, voluntary terminations, stillbirths, livebirths, and health of offspring. Reproductive hormones and testicular volume are assessed as described in the previous section.

*Evaluation of oral health and salivary secretion*

Oral health assessments are performed at the Copenhagen University Hospital. Endpoints include oral symptoms, impaired oral and dental health (mucosal changes, caries, erosions, gingivitis, periodontitis, malocclusions, temporomandibular dysfunction and salivary gland dysfunction) and changes in salivary microbiome and proteome. Questionnaire items include oral symptoms, current medication, dietary supplements, tobacco and alcohol consumption and oral hygiene habits. Xerostomia is assessed by means of the Bother Index[76], Xerostomia Inventory-8[77] and visual analogue scale (0-10)[78]. Additional evaluation of the oral health includes a clinical examination with palpation of the temporomandibular joint, salivary glands and regional lymph nodes; assessments of the morphological and functional occlusion, dental status (Decayed Missing Filled Teeth scores, dental erosion scores, dental malformations, delayed eruptions), periodontal status (gingival inflammation and dental plaque indices and assessment of periodontal probing depth) and mucosal status (mucosal changes and signs of dryness using Clinical Oral Dryness Score[79]). Unstimulated and chewing-stimulated whole saliva flow rates are measured according to the drooling method.[80] DNA is extracted from the saliva samples and the microbiome characterized by *HOMINGS* (Human Oral Microbe Identification using Next Generation Sequencing) with bacterial species-level identification based on 16S rDNA comparisons. Salivary proteome analyses are performed by means of 2-dimensional electrophoresis (2DE) and



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MALDI-TOF-MS (Matrix-Assisted Laser Desorption/Ionization Time-of-phFlight Mass Spectrometry). Western blot analysis and ELISA are used for validation of the 2DE results.

*Evaluation of other somatic health conditions*

Iron overload is evaluated with plasma levels of ferritin and transferrin saturation and with cardiac MRI T2* mapping. Hyper- and hypothyroidism is investigated with questionnaire data and measurement of thyroid stimulating hormone and free thyroxine. Hyperparathyroidism is evaluated with parathyroid hormone and total and ionized calcium. Additional health conditions specified in Table 1, but not described above, are evaluated using questionnaire data and medical chart validation as reported in Supplementary Table 1.

*Evaluation of mental health and quality of life*

Endpoints include psychiatric disease, social relations, emotional distress (anxiety, depression, and fatigue), executive function, and health-related quality of life. Questionnaire items include psychiatric diagnoses and psychopharmaceuticals. Additional psychosocial data are collected via instruments from Pediatric Quality of Life Inventory® (PedsQL), Patient Reported Outcomes Measurement Information System®(PROMIS), and the Behavior Rating Inventory of executive Function® (BRIEF) system. Specific instruments and versions are provided in Supplementary Table 4.

**Use of previously collected data for risk factor analysis**

ALL patient characteristics (date of diagnosis, tumor burden, immunophenotype, cytogenetics, minimal residual disease levels, final risk stratification, participation in protocol randomizations, and occurrence of 19 well-defined acute toxicities) are obtained from the NOPHO ALL2008 registry.[38] Medical chart data are used for validation of registered acute toxicities and for validation of self-reported health conditions (including dates). Genotyping for genome wide association studies (GWAS) has been performed previously on germline DNA from samples obtained after clinical remission using the exome-enriched Illumina Infinium Omni2.5exome-8- BeadChip arrays and is available for approximately 70% of the survivor population. Whole blood samples are collected from participants (including controls) not previously genotyped and samples are analyzed using the same platform.



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**Data management**

Study data were collected and managed using Research Electronic Data Capture (REDCap) tools hosted at Copenhagen University Hospital.[81,82] REDCap is a secure, web-based software platform designed to support data capture for research studies, providing 1) an intuitive interface for validated data capture; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for data integration and interoperability with external sources.

**Statistical considerations**

Cumulative incidence of the 197 health-conditions is calculated (individually and grouped according to organ system and severity grade) for survivors and controls and presented with 95% confidence intervals. Gray's test is used for comparison between the two groups. Cumulative burden of the 197 health-conditions is calculated (individually and grouped according to organ system and severity grades) in survivors and controls by the method of mean cumulative count, estimating the mean number of recurring or multiple health events in the presence of competing risk[83], and presented with 95% confidence intervals. For this purpose, health-conditions are categorized pre-analysis into three subtypes (chronic, non-recurrent; single, recurrent; and chronic, recurrent) based on clinical definitions of recurrence and chronicity, as described by others.[40] Based on a projected sample size of 250 survivors and 250 controls (survival rate of 90% in the Danish NOPHO ALL2008 patient cohort and a conservative recruitment rate of 60%), a 16% prevalence of chronic disease among Danish children[84], and significance level alpha=0.05, we will have a power of 87% to detect a hazard ratio (HR) of 2.0 in a Cox regression model, which is the lowest HR previously reported in a study comparing leukemia survivors with sibling controls.[85] Secondary outcomes (i.e. description of organ-specific functions) are compared between survivors and controls using relevant regression models (e.g. linear regression models, logistic regression models, or Cox regression models). For survivors, associations of primary and secondary outcomes with therapy exposure and occurrence of acute toxicities are explored using multiple regression models. Association with single nucleotide polymorphisms (SNP) is explored with genome-wide association analysis and using a candidate gene approach where relevant SNPs have been identified. Differences in demographics between survivor participants and non-participants are explored using Fischer's exact test for binary data and Student's/Welch's t-test or Wilcoxon rank sum test.



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**Patient Involvement**

In preparation of this study, we performed a qualitative interview study among adolescent and young adult NOPHO ALL2008 survivors to identify the challenges they perceive as most important.[18] Results from this study have been incorporated into the ALL-STAR examination program, securing focus on the issues most important to the survivors.

## 3. ETHICS AND DISSEMINATION

The study has been approved by the Regional Ethics Committee for the Capital Region in Denmark (no. H-18035090 and H-20006359), the Danish Data Protection Agency (no. VD-2018-519) and is conducted in accordance with the Helsinki Declaration. Written informed consent is obtained from all participants prior to enrollment. All participants can choose to participate in only parts of the study, can choose not to be informed of results, and can withdraw consent at any time. Study results will be published in international peer-reviewed scientific journals and presented at relevant conferences.

## 4. DISCUSSION

The ALL-STAR cohort is the first Nordic, population-based childhood and young adult ALL survivor cohort treated according to the same ALL protocol, to be uniformly evaluated for treatment-related morbidity across several organ systems, using both self-report data and objective, clinical investigations.

The evolution of long-term, adverse consequences of antileukemic therapy is complex and dependent not only on therapy exposure and genetic susceptibility, but also on age at diagnosis, preexisting morbidity, individual resources, resources among family and peers, and on surrounding health care- and societal structures. The Nordic countries differ from other western countries by complete and equal access to public health care, resulting in all pediatric cancer patients being treated and followed up in public hospitals and according to the same protocols. The comparison of a Nordic survivor cohort with survivor cohorts from other western countries will provide insight into the consequences of differing systems, as well as differences in treatment regimens used. Scandinavian countries, and particularly Denmark, have access to extensive register data including health- and socioeconomic information, linked to the individual person and surrounding network through personal identification numbers.[39] Coupling of systematic



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survivor data obtained in the ALL-STAR study to national register data will enable contextualizing association studies novel to survivorship research.

Strengths of the ALL-STAR study include a population-based design, a homogenous and well characterized cohort, the combination of both subjective and objective assessments of outcome, and inclusion of matched controls. The ALL-STAR cohort has already been characterized by prospective registration of tumor burden, immunophenotype, cytogenetics, treatment response, and occurrence of 19 severe toxicities, performed by treating physicians from time of diagnosis until end of therapy.[38] These data enable high precision evaluation of risk factors and confounders associated with our main outcome of interest. Similarly, high quality survivor data is secured through self-report data, medical chart validation, and systematic clinical examinations across most organ systems and using both well-established and novel, advanced techniques. This combination of data enables inclusion of survivor perspective while minimizing risk of recall bias and inaccurate information. Furthermore, the systematic screening of organ functions facilitates capture of low-grade conditions, which are likely to be underestimated if using retrospective or self-report data only.[40] Since the investigated health conditions are not pathognomic, the inclusion of matched controls, often missing in survivorship studies, will support conclusions made regarding the risk patterns which we seek to identify.

Despite vast amounts of late effects research being performed, no international consensus on how to characterize therapy-related late effects exist currently. Lack of precise definitions and uniform grading result in substantial variability across studies, hindering meaningful pooling and comparisons of results.[86] Cancer and therapy-related acute toxicities are traditionally defined and graded according to the CTCAE system and systematic modifications proposed by St Jude researchers has improved its utility for also addressing the long-term effects among childhood cancer survivors.[43] We have aligned our outcome definitions accordingly and by introducing ten additional health conditions of relevance for cancer survivorship research, we wish to further increase the relevance of this classification system.

The magnitude of late effects is often described with cumulative incidence; however, we encourage the use of the cumulative burden which includes recurrent events as opposed to only first events, thereby reflecting the burden more comprehensively. This is illustrated by a study investigating therapy-related cardiovascular conditions among survivors of childhood and young adult Hodgkin's lymphoma. By the age of 50, cumulative incidence of all grade cardiovascular health conditions did not differ between survivors and controls, while the cumulative burden of the



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same conditions was almost double in survivors compared to controls.[40] Since none of the measures, however, reflect survivor perspective, we have included the perceived impact of the individual health conditions, psychosocial function and health-related quality of life as reported by the participants. Coupling of objective findings with subjective survivor experiences is essential for interpretation of results and for guiding health-care workers and researchers when choosing which survivorship issues to prioritize.

There are several limitations to our study. A survival time of 3.5 – 14 years at evaluation means that the full spectrum of therapy-related conditions will not be captured. Establishment of the ALL-STAR cohort within the first decade of survival, however, forms the platform for longitudinal follow-up, which is within the overall scope of the project. Interpretation of initial data will be challenged by a heterogenous distribution in both age and survival time, but this will be adjusted for in the statistical analysis. Several of the health conditions evaluated in the ALL-STAR study rely on questionnaire data and subsequent medical chart validation. Low-grade conditions which are not screened for, are therefore likely to be missed. Finally, the ALL-STAR study outcomes are not exhaustive in describing the treatment-related burden. Important outcomes such as semen quality, ovarian reserve, and neurocognitive function were omitted to increase participation rates in the initial ALL-STAR initiative. Future studies of these important outcomes in the ALL-STAR cohort will benefit from the infrastructure already created.

In conclusion, the ALL-STAR study is establishing a Nordic childhood and young adult ALL survivor cohort to be systematically assessed for the cumulative incidence and burden of treatment-related morbidity. Results will supplement existing knowledge regarding risk of treatment-related morbidity and the underlying possible biological, physical and psychosocial mechanisms, while providing novel insight into differences in survivorship related to specific therapy regimens, health cultures and health care systems. Findings will guide future risk grouping and interventions during treatment and follow-up to ameliorate the burden of therapy without compromising chance of cure.

**List of abbreviations**

ALL = acute lymphoblastic leukemia; ALL-STAR = Acute Lymphoblastic Leukemia Survivor Toxicity And Rehabilitation; BMD = bone mineral density, BMI = body mass index; BRIEF® = Behavior Rating Inventory of executive Function®; CTCAE = Common Terminology Criteria for Adverse Events; DXA = dual-energy X-ray absorptiometry; ECG = electrocardiogram; FVC = forced vital capacity; GWAS = genome wide association studies; HRV = heart rate variability; MetS = metabolic syndrome; MRI = magnetic resonance imaging; NOPHO = Nordic Society of Pediatric Hematology



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and Oncology; PROMIS® = Patient Reported Outcomes Measurement Information System®; REDCap® = Research Electronic Data Capture; VO2peak = peak oxygen uptake

**DECLARATIONS**

**Patient consent for publication**

Not applicable

**Availability of data and materials**:

Generated data will be available after completion of the study upon reasonable request.

**Competing interests**

The authors declare that they have no competing interests.

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**Author contributions**

TLF, KS and LAJ devised the study concept and design. LAJ drafted the manuscript. All authors have contributed to developing the protocol, helped to write and review the manuscript, and made the decision to submit the manuscript for publication.

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**Figure 1. ALL-STAR Study overview.**
**Estimated survivors from 475 patients and overall survival rate of 90%.*
***Estimated number of participants based on minimum recruitment rate of 60%.*

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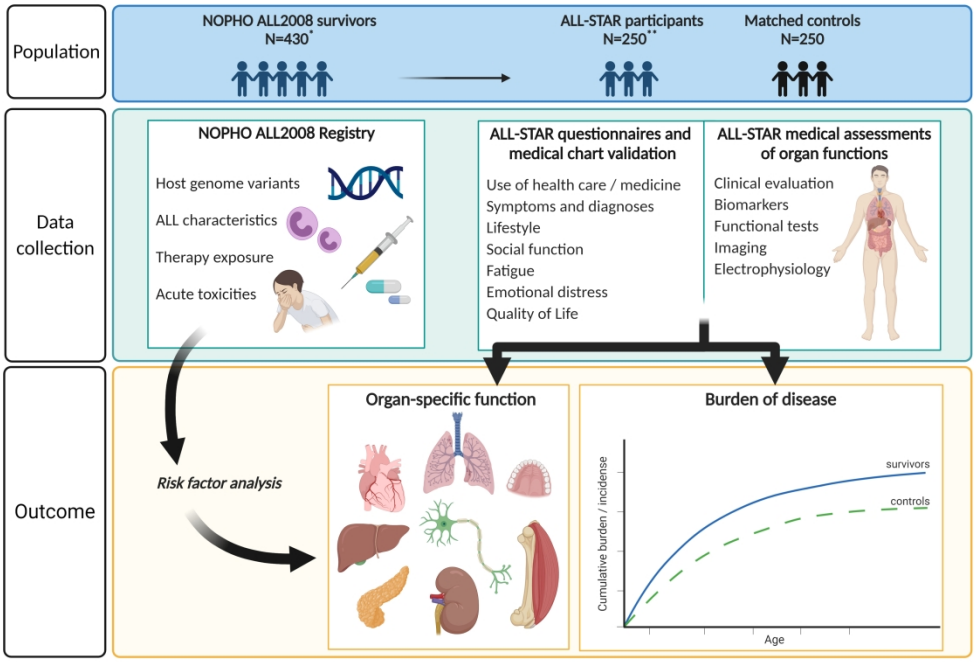


**Figure 1**. ALL-STAR study overview. **Estimated survivors from 475 patients and overall survival rate of 90%. **Estimated number of participants based on minimum recruitment rate of 60%.*

388x264mm (300 x 300 DPI)

**Supplementary table 1**. Definitions and grading of 197 health conditions evaluated in the ALL-STAR study according to the St Jude modified version[1] of the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) version 4.03[2]. Health conditions without available definitions from CTCAE v4.03 or the St Jude modified version are inserted with references if readily available and otherwise marked in *italic*.

| **AUDITORY-HEARING** | | | |
|---|---|---|---|
| **Health condition** | **Definition and Grading source** | **Grading** | **ALL-STAR data** |
| Cholesteatoma | Definition:<br>A mass formed by the keratinizing squamous epithelium in the middle ear and/or mastoid, subepithelial connective tissue and by the progressive accumulation of keratin debris with/without surrounding inflammatory reaction.[3]<br><br>Grading source:<br>St Jude modification of CTCAEv4.03<br>Ear and labyrinth disorders:<br>Other, specify | 1: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated<br>2: Moderate; minimal, local or non-invasive intervention indicated; limiting age appropriate instrumental ADL<br>3: Severe or medically significant but not immediately life threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self-care ADL<br>4: Life-threatening consequences; urgent intervention indicated<br>5: Death | - Questionnaire and medical record validation |
| Hearing loss | Definition:<br>A disorder characterized by partial or complete loss of the ability to detect or understand sounds resulting from damage to ear structures. Includes sensorineural, conductive and mixed hearing loss.<br><br>Grading source:<br>St Jude modification of CTCAEv4.03 Ear and labyrinth disorders: Hearing impaired.<br><br>St Jude Modified Chang Ototoxicity Grading Scale:<br><br>Chang KW, Chinosornvatana N. Practical grading system for evaluating cisplatin ototoxicity in children. J Clin Oncol 2010;28(10):1788-95. | 1: ≥ 40 dB at any frequency 6-12 kHz (Chang 1a); > 20 and < 40 dB at 4kHz (Chang 1b)<br>2: ≥ 40 dB at 4 kHz and above (Chang 2a); > 20 and < 40 dB at any frequency <4kHz (Chang 2b)<br>3: ≥ 40 dB at 2 or 3 kHz and above<br>4: ≥ 40 dB at 1 kHz and above<br>5: Not applicable | - Questionnaire and medical record validation |
| Tinnitus | Definition:<br>A disorder characterized by noise in the ears, such as ringing, buzzing, roaring or clicking<br><br>Grading source:<br>CTCAEv4.03<br>Ear and labyrinth disorders:<br>Tinnitus | 1: Mild symptoms; intervention not Indicated<br>2: Moderate symptoms; limiting instrumental ADL<br>3: Severe symptoms; limiting self-care ADL<br>4: Not applicable<br>5: Not applicable | - Questionnaire and medical record validation |

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| Vertigo | Definition:<br>A disorder characterized by a sensation as if the external world were revolving around the patient (objective vertigo) or as if he himself were revolving in space (subjective vertigo). Includes: Meniere's<br><br>Grading source:<br>CTCAEv4.03<br>Ear and labyrinth disorders:<br>Vertigo | 1: Mild symptoms; intervention not Indicated<br>2: Moderate symptoms; limiting instrumental ADL<br>3: Severe symptoms; limiting self-care ADL<br>4: Not applicable<br>5: Not applicable | - Questionnaire and medical record validation |
| **CARDIOVASCULAR** | | | |
| **Health condition** | **Definition and Grading source** | **Grading** | |
| Aortic root aneurysm | Definition:<br>A permanent localized dilation of the aortic artery having at least a 50% increase in diameter compared to the expected.[4]<br><br>Grading source:<br>St Jude modification of<br>CTCAE v4.03<br>Cardiac Disorders:<br>Other, specify | 1: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated (aortic root >= 3.5 cm to < 4 cm)<br>2: Moderate; minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental ADL (aortic root > = 4 cm)<br>3: Severe or medically significant but not immediately life threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self-care ADL<br>4: Life-threatening consequences; urgent intervention indicated<br>5: Death | - Questionnaire and medical record validation |
| Arteriovenous malformation | Definition:<br>*An abnormal connection between arteries and veins, bypassing the capillary system.*<br><br>Grading source:<br>CTCAE v4.03<br>Cardiac Disorders:<br>Other, specify | 1: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated<br>2: Moderate; minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental ADL<br>3: Severe or medically significant but not immediately life threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self-care ADL<br>4: Life-threatening consequences; urgent intervention indicated<br>5: Death | - Questionnaire and medical record validation |
| Atrioventricular heart block | Definition:<br>Includes: 1st degree (PR> 200msec), 2nd degree, Mobitz I, 2nd degree, Mobitz II, 3rd degree (complete) Bundle branch block, QRS > 120ms, Stokes-Adams Syndrome<br><br>Grading source:<br>CTCAE v4.03<br>Cardiac Disorders:<br>AV Block first degree (grades 1&2); AV block complete; Mobitz (type) II AV block; Mobitz type I (grades 3&4) | 1: Asymptomatic; intervention not indicated<br>2: Symptomatic; non-urgent medical intervention indicated<br>3: Symptomatic and incompletely controlled medically, or controlled with device (e.g., pacemaker)<br>4: Life-threatening consequences; urgent intervention indicated<br>5: Death | - Questionnaire and medical record validation<br>- Electrocardiogram |

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| Bradycardia, sinus | Definition:<br>A disorder characterized by a dysrhythmia with a heart rate less than 50 beats per minute that originates in the sinus node<br><br>Grading source<br>St Jude modification of<br>CTCAE v4.03<br>Cardiac Disorders:<br>Sinus bradycardia | 1: Asymptomatic; intervention not indicated<br>2: Symptomatic; medical intervention indicated<br>3: Severe; medically significant, medical intervention indicated<br>4: Life-threatening consequences; urgent intervention indicated<br>5: Death | - Questionnaire and medical record validation<br>- Electrocardiogram |
| Cardiopulmonary fitness, reduced | Definition:<br>The component of physiologic fitness relating to the ability of the cardiopulmonary system to supply oxygen during sustained physical activity. Reported as number of standard deviations (SD) from the expected mean, based on values from healthy controls.<br><br>Grading source:<br>ALL-STAR research team | 1: Symptomatic; shortness of breath during ADL and moderate physical activity perceived by the patient but not evident on physical exam<br>2: Symptomatic; reduced aerobic performance evident on physical exam; limiting instrumental ADL<br>3: Impaired aerobic performance limiting self-care ADL; < -1.96 SD of age and sex specific healthy control values<br>4: Not applicable<br>5: Not applicable | - Cardiopulmonary fitness test |
| Conduction abnormalities | Definition:<br>Includes: Sick Sinus Syndrome, Wolff-Parkinson-White syndrome<br><br>Grading source:<br>St Jude modification of<br>CTCAE v4.03<br>Cardiac Disorders:<br>Conduction disorder | 1: Asymptomatic or mild symptoms; intervention not indicated<br>2: Moderate symptoms; non-urgent intervention indicated<br>3: Severe symptoms; intervention indicated<br>4: Life-threatening consequences; urgent intervention indicated<br>5: Death | - Questionnaire and medical record validation<br>- Electrocardiogram |
| Congestive heart failure | Definition:<br>A disorder characterized by the inability of the heart to pump blood at an adequate volume to meet tissue metabolic requirements, or, the ability to do so only at an elevation in the filling pressure.<br><br>Grading source:<br>St Jude modification of<br>CTCAE v4.03<br>Cardiac Disorders:<br>Heart failure | 1: Asymptomatic with laboratory (e.g. BNP) or cardiac imaging abnormalities (NYHA I)<br>2: Symptoms with mild to moderate activity or exertion (NYHA II)<br>3: Severe with symptoms at rest or with minimal activity or exertion; intervention indicated (NYHA III)<br>4: Life-threatening consequences; urgent intervention indicated (e.g., continuous IV therapy or mechanical hemodynamic support (NYHA IV)<br>5: Death | - Questionnaire and medical record validation<br>- n-terminal pro brain natriuretic peptide (BNP)<br>- Electrocardiogram<br>- Speckle tracking echocardiography<br>- Cardiac MRI<br>- |

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| Coronary artery disease | Definition:<br>A disorder characterized by the inability of the heart to pump blood at an adequate volume to meet tissue metabolic requirements, or, the ability to do so only at an elevation in the filling pressure. Includes myocardial infarction.<br><br>Grading source:<br>St Jude modification of<br>CTCAE v4.03<br>Cardiac Disorders:<br>Myocardial infarction | 1: Asymptomatic; clinical or diagnostic observations only; intervention not indicated<br>2: Mild symptoms and cardiac enzymes minimally abnormal and no evidence of ischemic electrocardiogram changes<br>3: Severe symptoms; cardiac enzymes abnormal; hemodynamically stable; electrocardiogram changes consistent with infarction (Q waves)<br>4: Life-threatening consequences; hemodynamically unstable (CABG or angioplasty)<br>5: Death | - Questionnaire and medical record validation<br>- Troponin-T<br>- Electrocardiogram |
| Cor pulmonale (right heart failure) | Definition:<br>A disorder characterized by impairment of right ventricular function associated with low ejection fraction and a decrease in motility of the right ventricular wall<br><br>Grading source<br>CTCAE v4.03<br>Cardiac Disorders:<br>Right ventricular dysfunction | 1: Asymptomatic with laboratory (e.g., BNP) or cardiac imaging abnormalities<br>2: Symptoms with mild to moderate activity or exertion<br>3: Severe symptoms, associated with hypoxia, right heart failure; oxygen indicated<br>4: Life-threatening consequences; urgent intervention indicated (e.g., ventricular assist device); heart transplant indicated<br>5: Death | - Questionnaire and medical record validation<br>- n-terminal pro brain natriuretic peptide<br>- Speckle tracking echocardiography<br>- Cardiac MRI |
| Dysrhythmia | Definition:<br>A disorder characterized by a dysrhythmia originating above the ventricles. Includes: atrial fibrillation, atrial flutter, SVA, SVT, PAT; ventricular arrhythmia, and lethal arrhythmia requiring defibrillation.<br><br>Grading source:<br>CTCAE v4.03<br>Cardiac Disorders:<br>Atrial fibrillation | 1: Asymptomatic, intervention not indicated<br>2: Non-urgent medical intervention indicated<br>3: Symptomatic and incompletely controlled medically, or controlled with device (e.g., pacemaker), or ablation<br>4: Life-threatening consequences; urgent intervention indicated<br>5: Death | - Questionnaire and medical record validation<br>- Electrocardiogram |
| Heart valve disorder | Definition:<br>Disorders characterized by a defect in heart valve function or structure.<br><br>Grading source:<br>St Jude modification of<br>CTCAE v4.03<br>Cardiac Disorders:<br>Aortic valve disease; mitral valve disease; pulmonary valve disease; tricuspid valve disease | 1: Asymptomatic valvular thickening/calcifications with or without mild valvular regurgitation or stenosis by imaging<br>2: Asymptomatic; moderate regurgitation or stenosis by imaging<br>3: Symptomatic; severe regurgitation or stenosis by imaging; symptoms controlled with medical intervention<br>4: Life-threatening consequences; urgent intervention indicated (e.g., valve replacement, valvuloplasty)<br>5: Death | - Questionnaire and medical record validation<br>- Speckle tracking echocardiography<br>- Cardiac MRI |

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| High total cholesterol | Definition:<br>Higher than normal levels of cholesterol in a blood specimen<br><br>Grading source:<br>St Jude modification of CTCAE v4.03<br>Investigations:<br>Cholesterol high<br><br>ALL-STAR modification:<br>Units reported in SI-units, (100mg/dL = 2.59mmol/dL)[5]. | 1: >200 mg/dL - 300 mg/dL (>5.18 mmol/L–7.77 mmol/L)<br>2: >300 - 400 mg/dL (>7.77 mmol/L –10.36 mmol/L); treatment with one lipid lowering agent<br>3: >400 - 500 mg/dL (>10.36 mmol/L –12.95 mmol/L); treatment with >=2 lipid lowering agent<br>4: >500 mg/dL (>12.95 mmol/L)<br>5: Not applicable | | - Questionnaire and medical record validation<br>- Cholesterol level |
| Hypertension (from resting blood pressure) | Definition:<br>A disorder characterized by a pathological increase in blood pressure; a repeatedly elevation in the blood pressure<br><br>Grading source:<br>St Jude modification of CTCAE v4.03<br>Vascular Disorders:<br>Hypertension<br><br>Limits according to National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents.<br>Pediatrics. 2004;114(2 Suppl 4th Report):555. | Adult<br>1: Prehypertension (systolic BP 120 - 139 mm Hg or diastolic BP 80 - 89 mm Hg) | Pediatric<br>1: Prehypertension (systolic and/or diastolic BP >= 90th percentile but < 95th percentile for gender, age and height, or if in adolescents BP exceeds 120/80 mmHg even if <90th percentile) | - Questionnaire and medical record validation<br>- Blood pressure measurement |
| | | 2: Stage 1 hypertension (systolic BP 140 - 159 mm Hg or diastolic BP 90 - 99 mm Hg); medical intervention indicated or initiated; recurrent or persistent (>=24 hrs); symptomatic increase by >20 mm Hg (diastolic) or to >140/90 mm Hg if previously WNL; monotherapy indicated or initiated | 2: Stage 1 hypertension (systolic and/or diastolic BP between the 95th percentile and 5 mmHg above the 99th percentile for gender, age and height, or if in adolescents the BP exceeds 140/90 mmHg even <95th percentile); monotherapy indicated or initiated | |
| | | 3: Stage 2 hypertension (systolic BP >=160 mm Hg or diastolic BP >=100 mm Hg); medical intervention indicated; more than one drug or more intensive therapy than previously used indicated or initiated | 3: Stage 2 hypertension (systolic and/or diastolic BP ≥99th percentile plus 5 mmHg for gender, age, and height); more than one drug or more intensive therapy than previously used indicated or initiated | |
| | | 4: Life-threatening consequences (e.g., malignant hypertension, transient or permanent neurologic deficit, hypertensive crisis); urgent intervention indicated | 4: Life-threatening consequences (e.g., malignant hypertension, transient or permanent neurologic deficit, hypertensive crisis); urgent intervention indicated | |
| | | 5: Death | 5: Death | |

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| Hypertriglyceridemia | Definition:<br>A disorder characterized by laboratory test results that indicate an elevation in the concentration of triglyceride concentration in the blood<br><br>Grading source<br>St Jude modification of<br>CTCAE v4.03<br>Metabolism and Nutrition Disorders:<br>Hypertriglyceridemia<br><br>ALL-STAR modification:<br>Units reported as SI-units, (100mg/dL = 1.13mmol/L)[5] | 1: 150 mg/dL - 300 mg/dL (1.70 mmol/L–3.39 mmol/L)<br>2: >300 mg/dL - 500 mg/dL (>3.39 mmol/L – 5.65 mmol/L); treatment with one lipid lowering agent<br>3: >500 mg/dL - 1000 mg/dL (>5.65 mmol/L – 11.3mmol/L); treatment with >=2 lipid lowering agents<br>4: >1000 mg/dL (>11,3mmol/L); life-threatening consequences<br>5: Death | - Questionnaire and medical record validation<br><br>- Triglyceride level |
| Left ventricular systolic dysfunction | Definition:<br>A disorder characterized by failure of the left ventricle to produce adequate output despite an increase in distending pressure and in end-diastolic volume and reduced ejection fraction. Clinical manifestations may include dyspnea, orthopnea, and other signs and symptoms of pulmonary congestion and edema. Includes cardiomyopathy<br><br>Grading source:<br>St Jude modification of<br>CTCAE v4.03<br>Investigations: Ejection fraction decreased (grades 2&3)<br>Left ventricular systolic dysfunction (grade 4) | 1: Not applicable<br>2: Resting EF < 50-40%; 10 - 19% absolute drop from baseline<br>3: Resting EF 39-20%; >20% absolute drop from baseline; medication indicated or initiated<br>4: Resting EF<20%; refractory or poorly controlled heart failure due to drop in ejection fraction; on medical management; intervention such as ventricular assist device, intravenous vasopressor support, or heart transplant indicated<br>5: Death | - Questionnaire and medical record validation<br>- Speckle tracking echocardiography<br>- Cardiac MRI |
| Pericarditis | Definition:<br>A disorder characterized by irritation to the layers of the pericardium (the protective sac around the heart).<br><br>Grading source:<br>St Jude modification of<br>CTCAE v4.03<br>Cardiac Disorders:<br>Pericarditis | 1: Asymptomatic, electrocardiogram or physical findings (e.g., rub) consistent with pericarditis<br>2: Symptomatic pericarditis (e.g., chest pain)<br>3: Pericarditis with physiologic consequences (e.g., pericardial constriction)<br>4: Life-threatening consequences; urgent intervention indicated (e.g., cardiac tamponade)<br>5: Death | - Questionnaire and medical record validation<br>- Electrocardiogram |

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| Prolonged QTcorrected (QTc) interval | Definition:<br>A finding of a cardiac dysrhythmia characterized by an abnormally long corrected QT interval<br><br>Grading source:<br>St Jude modification of CTCAE v4.03<br>Investigations:<br>Prolonged QTc interval | 1: QTc 460 - 480 ms (men); 470-480 ms (women)<br>2: QTc 481 - 500 ms<br>3: QTc >= 501 ms on >= two separate electrocardiograms<br>4: QTc >= 501 or >60 ms change from baseline and Torsade de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia<br>5: Not applicable | - Questionnaire and medical record validation<br>- Electrocardiogram |
| Pulmonary hypertension | Definition:<br>A disorder characterized by an increase in pressure within the pulmonary circulation due to lung or heart disorder<br><br>Grading source:<br>CTCAE v4.03<br>Respiratory, thoracic, and mediastinal disorders:<br>Pulmonary hypertension | 1: Minimal dyspnea; findings on physical exam or other evaluation<br>2: Moderate dyspnea, cough; requiring evaluation by cardiac catheterization and medical intervention<br>3: Severe symptoms, associated with hypoxemia, right heart failure; oxygen indicated<br>4: Life-threatening airway consequences; urgent intervention indicated (e.g., tracheotomy or intubation)<br>5: Death | - Questionnaire and medical record validation<br>- Speckle tacking echocardiography |
| Raynaud phenomenon | Definition:<br>A clinical disorder consisting of recurrent, long-lasting, and episodic vasospasm of the fingers and toes (rarer in tongue, nose, ears, nipples) often associated with exposure to cold.[6]<br><br>Grading source:<br>St Jude modification of CTCAE v4.03<br>Vascular Disorders:<br>Other, specify | 1: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated<br>2: Moderate; minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental ADL<br>3: Severe or medically significant but not immediately life threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self-care ADL<br>4: Life-threatening consequences; urgent intervention indicated<br>5: Death | - Questionnaire, COMPASS31 and medical record validation |
| Right ventricular systolic dysfunction | Definition:<br>A disorder characterized by impairment of right ventricular function associated with low ejection fraction and a decrease in motility of the right ventricular wall<br><br>Grading source:<br>St Jude modification of CTCAE v4.03<br>Cardiac Disorders:<br>Right ventricular dysfunction | 1: Asymptomatic cardiac imaging abnormalities<br>2: Symptoms with mild to moderate activity or exertion<br>3: Severe symptoms, associated with hypoxia, right heart failure; oxygen indicated<br>4: Life-threatening consequences; urgent intervention indicated (e.g., ventricular assist device); heart transplant indicated<br>5: Death | - Questionnaire and medical record validation<br>- Speckle tacking echocardiography<br>- Cardiac MRI |

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| Tachycardia, sinus | Definition:<br>A disorder characterized by a dysrhythmia with a heart rate greater than 100 beats per minute for adults and greater than 110 beats per minute for children that originates in the sinus node<br><br>Grading source:<br>St Jude modification of CTCAE v4.03<br>Cardiac Disorders:<br>Sinus tachycardia | 1: Asymptomatic, intervention not indicated<br>2: Symptomatic; non-urgent medical intervention indicated<br>3: Urgent medical intervention indicated<br>4: Not applicable<br>5: Not applicable | - Questionnaire and medical record validation<br>- Electrocardiogram |
| Thromboembolic event | Definition:<br>A disorder characterized by occlusion of a vessel by a thrombus that has migrated from a distal site via the blood stream.<br><br>Grading source:<br>St Jude modification of CTCAE v4.03<br>Vascular Disorders: Thromboembolic event | 1: Venous thrombosis (e.g., superficial thrombosis)<br>2: Venous thrombosis (e.g., uncomplicated deep vein thrombosis), medical intervention indicated<br>3: Thrombosis (e.g., non-embolic cardiac mural [arterial] thrombus), medical intervention indicated<br>4: Life-threatening (e.g., cerebrovascular event, arterial insufficiency); hemodynamic or neurologic instability; urgent intervention indicated<br>5: Death | - Questionnaire and medical record validation |
| Vascular disease | Definition:<br>Stenosis/occlusion of vessel other than coronary or cerebral vessels, e.g., carotid, subclavian.<br><br>Grading source:<br>St Jude modification of CTCAE v4.03<br>Vascular Disorders<br>Other, specify | 1: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated<br>2: Moderate; minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental ADL<br>3: Severe or medically significant but not immediately life threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self-care ADL<br>4: Life-threatening consequences; urgent intervention indicated<br>5: Death | - Questionnaire and medical record validation |
| **ENDOCRINE** | | | |
| **Health condition** | **Definition and Grading source** | **Grading** | **Data Grading source** |
| Abnormal glucose metabolism | Definition:<br>A disorder characterized by an inability to properly metabolize glucose. Includes impaired fasting glucose, insulin resistance with impaired glucose tolerance, diabetes mellitus.<br><br>Grading source:<br>St Jude modification of CTCAE v4.03<br>Metabolism and nutrition disorders:<br>Glucose intolerance | 1: Asymptomatic; clinical or diagnostic observations only; pharmacologic intervention not indicated or initiated (e.g. dietary modification)<br>2: Symptomatic; oral agent indicated or initiated<br>3: Severe symptoms; insulin indicated or initiated<br>4: Life threatening consequences, urgent intervention indicated or initiated<br>5: Death | - Questionnaire and medical record validation<br>- Fasting-glucose<br>- HOMA-IR |

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| Adrenal insufficiency | Definition:<br>A disorder that occurs when the adrenal cortex does not produce enough of the hormone cortisol and in some cases, the hormone aldosterone. It may be due to a disorder of the adrenal cortex as in Addison's disease or primary adrenal insufficiency.<br><br>Grading source:<br>St Jude modification of CTCAE v4.03<br>Endocrine disorders:<br>Adrenal insufficiency | 1: Asymptomatic; clinical or diagnostic observations only; intervention indicated during periods of stress<br>2: Moderate symptoms; daily maintenance indicated (i.e. am cortisol < 5 mcg/dL) or initiated<br>3: Severe symptoms; hospitalization indicated<br>4: Life-threatening consequences; urgent intervention indicated<br>5: Death | - Questionnaire and medical record validation |
| Adult growth hormone deficiency | Definition:<br>A finding based on laboratory test results that indicate abnormal levels of growth hormone in a biological specimen<br><br>Grading source:<br>St Jude modification of CTCAE v4.03<br>Investigations:<br>Growth hormone abnormal | 1: Asymptomatic; clinical or diagnostic observations only; intervention not indicated (IGF-1 z-score < -2 in isolation or abnormal dynamic test with decision not to pursue treatment)<br>2: Symptomatic; medical intervention indicated; limiting instrumental ADL<br>3: Not applicable<br>4: Not applicable<br>5: Not applicable | - Questionnaire and medical record validation |
| Childhood growth hormone deficiency | Definition:<br>A finding based on laboratory test results that indicate abnormal levels of growth hormone in a biological specimen<br><br>Grading source:<br>St Jude modification of CTCAE v4.03<br>Investigations:<br>Growth hormone abnormal | 1: Asymptomatic; clinical or diagnostic observations only; intervention not indicated (abnormal dynamic test with decision not to pursue treatment)<br>2: Symptomatic; medical intervention indicated; limiting instrumental ADL<br>3: Not applicable<br>4: Not applicable<br>5: Not applicable | - Questionnaire and medical record validation |
| Diabetes insipidus | Definition:<br>A form of polyuria–polydipsia syndrome characterized by hypotonic polyuria and polydipsia.[7]<br><br>Grading source:<br>St Jude modification of CTCAE v4.03.<br>Endocrine disorders:<br>Other, specify | 1: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated<br>2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL<br>3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self-care ADL<br>4: Life-threatening consequences; urgent intervention indicated<br>5: Death | - Questionnaire and medical record validation |

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| Growth hormone excess | Definition:<br>A finding based on laboratory test results that indicate abnormal levels of growth hormone in a biological specimen<br><br>Grading source:<br>St Jude modification of CTCAE v4.03.<br>Investigations: Growth hormone abnormal | 1: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated<br>2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL<br>3: Death Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self-care ADL<br>4: Life-threatening consequences; urgent intervention indicated<br>5: Death | - Questionnaire and medical record validation |
| Hyperparathyroidism | Definition:<br>A disorder characterized by an increase in production of parathyroid hormone by the parathyroid glands. This results in hypercalcemia (abnormally high levels of calcium in the blood).<br><br>Grading source:<br>St Jude modification of<br>CTCAE v4.03. Endocrine disorders: Hyperparathyroidism | 1: Mild symptoms; intervention not indicated<br>2: Moderate symptoms; medical intervention indicated or initiated<br>3: Not applicable<br>4: Not applicable<br>5: Not applicable | - Questionnaire and medical record validation<br>- Parathyroid hormone<br>- Ionized calcium |
| Hyperprolactinemia | Definition:<br>A disorder of mineral metabolism due to excessive secretion of parathyroid hormone from one or more of the four parathyroid glands.[8]<br><br>Grading source:<br>St Jude modification of<br>CTCAE v4.03. Endocrine disorders: Other, specify | 1: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated<br>2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL<br>3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self-care ADL<br>4: Life-threatening consequences; urgent intervention indicated<br>5: Death | - Questionnaire and medical record validation |
| Hyperthyroidism | Definition:<br>A disorder characterized by excessive levels of thyroid hormone in the body. Common causes include an overactive thyroid gland or thyroid hormone overdose<br><br>Grading source:<br>St Jude modification of<br>CTCAE v4.03<br>Endocrine disorders: Hyperthyroidism | 1: Asymptomatic; clinical or diagnostic observations only; intervention not indicated<br>2: Symptomatic; thyroid suppression indicated or initiated; limiting instrumental ADL<br>3: Severe symptoms; limiting self-care ADL; hospitalization indicated<br>4: Life-threatening consequences; urgent intervention indicated<br>5: Death | - Questionnaire and medical record validation<br>- Thyroid stimulating hormone<br>- Triiodothyronine |

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| Hypoparathyroidism | Definition:<br>A disorder characterized by a decrease in production of parathyroid hormone by the parathyroid glands.<br><br>Grading source:<br>St Jude modification of<br>CTCAE v4.03<br>Endocrine disorders: Hypoparathyroidism | 1: Asymptomatic; clinical or diagnostic observations only; intervention not indicated<br>2: Moderate symptoms; medical intervention indicated or initiated<br>3: Severe symptoms; medical intervention or hospitalization indicated<br>4: Life-threatening consequences; urgent intervention indicated<br>5: Death | | - Questionnaire and medical record validation<br>- Parathyroid hormone<br>- Ionized calcium |
| Hypothyroidism | Definition:<br>A disorder characterized by a decrease in production of thyroid hormone by the thyroid gland. Includes compensated hypothyroidism.<br><br>Grading source:<br>St Jude modification of<br>CTCAE v4.03<br>Endocrine disorders:<br>Hypothyroidism | 1: Asymptomatic; clinical or diagnostic observations only; intervention not indicated (compensated hypothyroidism)<br>2: Symptomatic; thyroid replacement indicated or initiated; limiting instrumental ADL<br>3: Severe symptoms; limiting self- care ADL; hospitalization indicated<br>4: Life-threatening consequences; urgent intervention indicated<br>5: Death | | - Questionnaire and medical record validation<br>- Thyroid stimulating hormone<br>- Triiodothyronine |
| Overweight/Obesity | Definition:<br>A disorder characterized by having a high amount of body fat. Grading source for < 20 years: Criteria per Centers for Disease Control and Prevention guidelines<br><br>Grading source:<br>St Jude modification of<br>CTCAE v4.03<br>Metabolism and nutrition disorders: Obesity<br><br>ALL-STAR modification:<br>Pediatric Grading source according to National, Danish norm material[9]. | For age >= 20 years<br>1: Not applicable<br>2: BMI 25 - 29.9 kg/m2<br>3: BMI 30 - 39.9 kg/m2<br>4: BMI >=40 kg/m2<br>5: Not applicable | For age 2 - <20 years<br>1: Not applicable<br>2: BMI >= 85$^{th}$%ile <95$^{th}$%ile<br>3: BMI $\geq$ 95$^{th}$%ile<br>4: Not applicable<br>5: Not applicable<br><br>ALL-STAR modification:<br>1: Not applicable<br>2: BMI > +1 < +2 standard deviations (84.1%-97.7%)<br>3: BMI > +2 standard deviations (>97.7%)<br>4,5: NA | - Questionnaire and medical record validation<br>- Weight<br>- Height |

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| Sarcopenic obesity | Definition<br>High body fat percentage (BF%) and/or high android fat percentage (AF%) and/or high android/gynoid fat distribution ratio (AG ratio).<br><br>Grading source:<br>ALL-STAR research team<br><br>Standard deviations used for grading are based on results from matched ALL-STAR controls and on the following available sources:<br><br><u>BF% in children:</u><br>Wohlfahrt-Veje et al. Body fat throughout childhood in 2647 healthy Danish children: Agreement of BMI, waist circumference, skinfolds with dual X-ray absorptiometry. Eur J Clin Nutr. 2014;68(6):664–70.<br><br><u>AF% in children:</u><br>Tinggaard J et al. Anthropometry, DXA, and leptin reflect subcutaneous but not visceral abdominal adipose tissue on MRI in 197 healthy adolescents. Pediatr Res. 2017 Oct 1;82(4):620–8.<br><br><u>BF% and AG ratio in adults:</u><br>Miazgowski T et al. Visceral fat reference values derived from healthy European men and women aged 20-30 years using GE Healthcare dual-energy x-ray absorptiometry. PLoS One. 2017 Jul 1;12(7). | 1: Not applicable<br>2: BF% > +1 standard deviations (SD) < +2 SD OR AG > +1 standard deviations (SD) < +2 SD<br>3: BF% > +2 SD OR AG > +2SD<br>4: Not applicable<br>5: Not applicable | 1: Not applicable<br>2: BF% > +1 standard deviations (SD) < +2 SD OR AF% > +1 standard deviations (SD) < +2 SD<br>3: BF% > +2 SD OR AF% > +2SD<br>4: Not applicable<br>5: Not applicable | - DEXA body composition scans |
| Syndrome of inappropriate antidiuretic hormone secretion | Definition:<br>A syndrome characterized by hyponatremia and renal salt loss, unrelated to either renal or adrenal disease, but attributed to overexpansion of body fluids resulting from inappropriate secretion of antidiuretic hormone (ADH).[10]<br><br>Grading source:<br>St Jude modification of CTCAE v4.03<br>Endocrine disorders:<br>Other, specify | 1: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated<br>2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL<br>3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self-care ADL<br>4: Life-threatening consequences; urgent intervention indicated<br>5: Death | | - Questionnaire and medical record validation |

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| Underweight | Definition:<br>Low weight compared to the expected for age and height<br><br>Grading source:<br>St Jude introduced category. Grading source: Criteria per Centers for Disease Control and Prevention guidelines<br><br>ALL-STAR modification:<br>BMI limit expressed as number of standard deviations from the expected mean, based on national Danish reference material[9] | For age >= 20 years<br>1: Not applicable<br>2: BMI < 18.5 kg/m2<br>3: Not applicable<br>4: Not applicable<br>5: Not applicable | For age 2 -< 20 years<br>1: Not applicable<br>2: BMI < 5$^{th}$%ile (< -2SD = <2.3%le)<br>3: Not applicable<br>4: Not applicable<br>5: Not applicable | - Questionnaire and medical record validation<br>- Weight<br>- Height |
| **GASTROINTESTINAL** | | | | |
| **Health condition** | **Definition and Grading source** | **Grading** | | **Data Grading source** |
| Bowel perforation | Definition:<br>A disorder characterized by a rupture in the small intestine wall.<br><br>Grading source:<br>St Jude modification of CTCAEv4.03 Gastrointestinal disorders:<br>Small intestinal perforation | 1: Not applicable<br>2: Symptomatic; medical intervention indicated<br>3: Severe symptoms; elective operative intervention indicated<br>4: Life-threatening consequences; urgent operative intervention indicated<br>5: Death | | - Questionnaire and medical record validation |
| Celiac disease | Definition:<br>An autoimmune disorder occurring in genetically predisposed individuals who develop an immune reaction to gluten.[11]<br><br>Grading source:<br>St Jude modification of CTCAEv4.03 Gastrointestinal disorders:<br>Other, specify | 1: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated<br>2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL<br>3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self-care ADL<br>4: Life-threatening consequences; urgent intervention indicated<br>5: Death | | - Questionnaire and medical record validation |
| Constipation | Definition:<br>A disorder characterized by irregular and infrequent or difficult evacuation of the bowels.<br><br>Grading source:<br>St Jude modification of CTCAEv4.03 Gastrointestinal disorders:<br>Constipation | 1: Not applicable<br>2: Persistent symptoms with regular use of laxatives or enemas; limiting instrumental ADL<br>3: Obstipation with manual evacuation indicated; limiting self-care ADL<br>4: Life-threatening consequences; urgent intervention indicated<br>5: Death | | - Questionnaire, COMPASS31 and medical record validation |

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| Dysphagia | Definition:<br>A disorder characterized by difficulty in swallowing<br><br>Grading source:<br>CTCAEv4.03<br>Gastrointestinal disorders:<br>Dysphagia | 1: Symptomatic, able to eat regular diet<br>2: Symptomatic and altered eating or swallowing<br>3: Severely altered eating or swallowing; tube feeding or TPN or hospitalization indicated<br>4: Life-threatening consequences; urgent intervention indicated<br>5: Death | - Questionnaire and medical record validation |
| Enterocolitis | Definition:<br>A disorder characterized by inflammation of the small and large intestines. Includes: ileitis, typhlitis, colitis, enterocolitis, diverticulitis, Crohn's disease, ulcerative colitis.<br><br>Grading source:<br>St Jude modification of CTCAEv4.03<br>Gastrointestinal disorders:<br>Enterocolitis | 1: Asymptomatic; clinical or diagnostic observations only; intervention not indicated<br>2: Abdominal pain; mucus or blood in stool<br>3: Severe or persistent abdominal pain; fever; ileus; peritoneal signs<br>4 Life-threatening consequences; urgent intervention indicated<br>5: Death | - Questionnaire and medical record validation |
| Esophageal varices | Definition:<br>A disorder characterized by bleeding from esophageal varices<br><br>Grading source:<br>CTCAEv4.03<br>Gastrointestinal disorders:<br>Esophageal varices hemorrhage | 1: Not applicable<br>2: Self-limited; intervention not indicated<br>3: Transfusion, radiologic, endoscopic, or elective operative intervention indicated<br>4: Life-threatening consequences; urgent intervention indicated<br>5: Death | - Questionnaire and medical record validation |
| Esophagitis | Definition:<br>A disorder characterized by inflammation of the esophageal wall.<br><br>Grading source:<br>CTCAEv4.03<br>Gastrointestinal disorders:<br>Esophagitis | 1: Asymptomatic; clinical or diagnostic observations only; intervention not indicated<br>2: Symptomatic; altered eating/swallowing; oral supplements indicated<br>3: Severely altered eating/swallowing; tube feeding, TPN or hospitalization indicated<br>4: Life-threatening consequences; urgent operative intervention indicated<br>5: Death | - Questionnaire and medical record validation |
| Fecal incontinence | Definition:<br>A disorder characterized by inability to control the escape of stool from the rectum.<br><br>Grading source:<br>CTCAEv4.03<br>Gastrointestinal disorders:<br>Fecal incontinence | 1: Occasional use of pads required<br>2: Daily use of pads required<br>3: Severe symptoms; elective operative intervention indicated<br>4: Not applicable<br>5: Not applicable | - Questionnaire, COMPASS31 and medical record validation |

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| Gastritis/duodenitis | Definition:<br>A disorder characterized by inflammation of the stomach<br><br>Grading source:<br>St Jude modification of CTCAEv4.03<br>Gastrointestinal disorders:<br>Gastritis | 1: Asymptomatic; clinical or diagnostic observations only; intervention not indicated<br>2: Symptomatic; altered GI function; medical intervention indicated<br>3: Severely altered eating or gastric function; TPN or hospitalization indicated<br>4: Life-threatening consequences; urgent operative intervention indicated<br>5: Death | - Questionnaire and medical record validation |
| Gastroesophageal reflux disease | Definition:<br>A disorder characterized by reflux of the gastric and/or duodenal contents into the distal esophagus. It is chronic in nature and usually caused by incompetence of the lower esophageal sphincter and may result in injury to the esophageal mucosal. Symptoms include heartburn and acid indigestion.<br><br>Grading source:<br>CTCAEv4.03<br>Gastrointestinal disorders:<br>Gastroesophageal reflux disease | 1: Mild symptoms; intervention not indicated<br>2: Moderate symptoms; medical intervention indicated<br>3: Severe symptoms; surgical intervention indicated<br>4: Not applicable<br>5: Not applicable | - Questionnaire and medical record validation |
| Gastrointestinal fistulas | Definition:<br>A disorder characterized by an abnormal communication between any part of the gastrointestinal system and another organ or anatomic site<br><br>Grading source:<br>CTCAEv4.03<br>Gastrointestinal disorders:<br>Gastrointestinal fistula | 1: Asymptomatic; clinical or diagnostic observations only; intervention not indicated<br>2: Symptomatic; altered GI function<br>3: Severely altered GI function; tube feeding, TPN or hospitalization indicated; elective operative intervention indicated<br>4: Life-threatening consequences; urgent operative intervention indicated<br>5: Death | - Questionnaire and medical record validation |
| Gastrointestinal hemorrhage | Definition:<br>A disorder characterized by bleeding from the upper/lower gastrointestinal tract (oral cavity, pharynx, esophagus, and stomach, small intestine, large intestine, and anus).<br><br>Grading source:<br>St Jude modification of CTCAEv4.03<br>Gastrointestinal disorders:<br>Upper/Lower gastrointestinal hemorrhage | 1: Mild; intervention not indicated<br>2: Moderate symptoms; medical intervention or minor cauterization indicated<br>3: Transfusion; invasive intervention indicated (e.g. radiologic, endoscopic, or elective operative interventions)<br>4: Life-threatening consequences; urgent intervention indicated<br>5: Death | - Questionnaire and medical record validation |

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| Gastrointestinal necrosis | Definition:<br>A disorder characterized by a necrotic process occurring in the gastric/intestinal wall.<br><br>Grading source:<br>St Jude modification of CTCAEv4.03<br>Gastrointestinal disorders:<br>Gastric necrosis | 1: Not applicable<br>2: Not applicable<br>3: Inability to aliment adequately by GI tract; radiologic, endoscopic, or operative intervention indicated<br>4: Life-threatening consequences; urgent operative intervention indicated<br>5: Death | - Questionnaire and medical record validation |
| Gastrointestinal obstruction | Definition:<br>A disorder characterized by blockage of the normal flow of the intestinal contents.<br><br>Grading source:<br>St Jude modification of CTCAEv4.03<br>Gastrointestinal disorders:<br>Small intestinal obstruction | 1: Asymptomatic; clinical or diagnostic observations only; intervention not indicated<br>2: Symptomatic; altered GI function; limiting instrumental ADL<br>3: Hospitalization indicated; elective operative intervention indicated; limiting self -are ADL; disabling<br>4: Life-threatening consequences; urgent operative intervention indicated<br>5: Death | - Questionnaire and medical record validation |
| Gastrointestinal strictures | Definition:<br>A disorder characterized by a narrowing of the lumen of the esophagus/stomach/intestines<br><br>Grading source:<br>St Jude modification of CTCAEv4.03<br>Gastrointestinal disorders:<br>Esophageal stenosis | 1: Asymptomatic; clinical or diagnostic observations only; intervention not indicated<br>2: Symptomatic; altered GI function<br>3: Severely altered GI function; tube feeding; hospitalization indicated; elective operative intervention indicated<br>4: Life-threatening consequences; urgent operative intervention indicated<br>5: Death | - Questionnaire and medical record validation |
| Gastrointestinal ulcer | Definition:<br>A disorder characterized by a circumscribed, inflammatory and necrotic erosive lesion on the mucosal surface of the stomach/intestines<br><br>Grading source:<br>St Jude modification of CTCAEv4.03<br>Gastrointestinal disorders:<br>Gastric ulcer | 1: Asymptomatic; clinical or diagnostic observations only; intervention not indicated<br>2: Symptomatic; altered GI function; medical intervention indicated; limiting instrumental ADLs<br>3: Severely altered GI function; TPN indicated; invasive intervention indicated (e.g. elective operative or endoscopic intervention); limiting self-care ADL; disabling<br>4: Life-threatening consequences; urgent operative intervention indicated<br>5: Death | - Questionnaire and medical record validation |

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| Gastroparesis syndrome | Definition:<br>A chronic disorder characterized by delayed emptying of the stomach after eating, in the absence of any mechanical obstruction.[12]<br><br>Grading source:<br>CTCAEv4.03<br>Gastrointestinal disorders:<br>Gastroparesis | 1: Mild nausea, early satiety and bloating, able to maintain caloric intake on regular diet<br>2: Moderate symptoms; able to maintain nutrition with dietary and lifestyle modifications; may need pharmacologic intervention<br>3: Weight loss; refractory to medical intervention; unable to maintain nutrition orally<br>4: Not applicable<br>5: Not applicable | - Questionnaire, COMPASS31, and medical record validation |
| Malabsorption syndrome | Definition:<br>A disorder characterized by inadequate absorption of nutrients in the small intestine. Symptoms include abdominal marked discomfort, bloating and diarrhea<br><br>Grading source<br>CTCAEv4.03<br>Gastrointestinal disorders:<br>Malabsorption | 1: Not applicable<br>2: Altered diet; oral intervention Indicated<br>3: Inability to aliment adequately; TPN indicated<br>4: Life-threatening consequences; urgent intervention indicated<br>5: Death | - Questionnaire and medical record validation |
| Pancreatic insufficiency | Definition:<br>A finding based on laboratory test results that indicate a decrease in levels of pancreatic enzymes in a biological specimen.<br><br>Grading source:<br>CTCAEv4.03<br>Investigations:<br>Pancreatic enzymes decreased | 1: <LLN and asymptomatic<br>2: Increase in stool frequency, bulk, or odor; steatorrhea<br>3: Sequelae of absorption deficiency<br>4: Not applicable<br>5: Not applicable | - Questionnaire and medical record validation<br>- Fecal elastase |
| Pancreatitis | Definition:<br>A disorder characterized by inflammation of the pancreas<br><br>Grading source:<br>CTCAEv4.03<br>Gastrointestinal disorders:<br>Pancreatitis | 1: Not applicable<br>2: Enzyme elevation or radiologic findings only<br>3: Severe pain; vomiting; medical intervention indicated (e.g., analgesia, nutritional support)<br>4: Life-threatening consequences; urgent intervention indicated<br>5: Death | - Questionnaire and medical record validation<br>- Amylase<br>- Lipase<br>- Ultrasound examination of pancreas |
| Proctitis | Definition:<br>A disorder characterized by inflammation of the rectum.<br><br>Grading source:<br>CTCAEv4.03<br>Gastrointestinal disorders:<br>Proctitis | 1: Rectal discomfort, intervention not indicated<br>2: Symptoms (e.g., rectal discomfort, passing blood or mucus); medical intervention indicated; limiting instrumental ADL<br>3: Severe symptoms; fecal urgency or stool incontinence; limiting self-care ADL<br>4: Life-threatening consequences; urgent intervention indicated<br>5: Death | - Questionnaire and medical record validation |

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| HEPATOBILIARY | | | |
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| **Health condition** | **Definition and Grading source** | **Grading** | **Data Grading source** |
| Cholecystitis/<br>Cholelithiasis | Definition:<br>A disorder characterized by inflammation involving the gallbladder. It may be associated with the presence of gallstones<br><br>Grading source:<br>St Jude modification of CTCAEv4.03<br>Hepatobiliary disorders:<br>Cholecystitis | 1: Not applicable<br>2: Symptomatic; medical intervention indicated<br>3: Severe symptoms; invasive intervention indicated (e.g. radiologic, endoscopic or elective operative intervention)<br>4: Life-threatening consequences; urgent operative intervention indicated<br>5: Death | - Questionnaire and medical record validation |
| Fibrosis/Cirrhosis | Definition:<br>A condition resulting from liver injury leading to necroinflammation and fibrogenesis.[13] Includes patients with Hepatitis B and Hepatitis C induced cirrhosis.<br><br>Grading source:<br>Category and grading according to St Jude<br><br>ALL-STAR modification:<br>ultrasound shear wave elastography (USWE) added | 1: Not applicable<br>2: Not applicable<br>3: Compensated USWE proven or biopsy proven fibrosis/cirrhosis (e.g. asymptomatic thrombocytopenia)<br>4: Decompensated USWE proven or biopsy proven fibrosis/cirrhosis (e.g., coagulopathy, encephalopathy, coma, variceal hemorrhage)<br>5: Death | - Questionnaire and medical record validation<br>- Liver enzymes, INR, albumin, platelets<br>- Hepatic ultrasound including USWE and evaluation of spleen |
| Hepatic failure | Definition:<br>A disorder characterized by the inability of the liver to metabolize chemicals in the body. Laboratory test results reveal abnormal plasma levels of ammonia, bilirubin, lactic dehydrogenase, and alkaline phosphatase.<br><br>Grading source:<br>St Jude modification of CTCAEv4.03<br>Gastrointestinal disorders:<br>Hepatic failure | 1: Not applicable<br>2: Not applicable<br>3: Asterixis; mild encephalopathy; limiting self-care ADL<br>4: Moderate to severe encephalopathy; coma; life threatening consequences; requiring liver transplantation<br>5: Death | - Questionnaire and medical record validation<br>- Liver enzymes, INR, albumin, platelets, bilirubin, LDH |

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| Hepatopathy | Definition:<br>A finding based on laboratory test results that indicate an increase in the level of aspartate aminotransferase (AST or SGOT) and alanine aminotransferase (AST or SGPT) in a blood specimen<br><br>Grading source:<br>CTCAEv4.03<br>Investigations:<br>Alanine and aspartate aminotransferase Increased | 1: >ULN - 3.0 x ULN<br>2: >3.0 - 5.0 x ULN<br>3: >5.0 - 20.0 x ULN<br>4: >20.0 x ULN<br>5: Not applicable | - Questionnaire and medical record validation<br>- Liver enzymes |
| Portal hypertension | Definition:<br>A disorder characterized by an increase in blood pressure in the portal venous system.<br><br>Grading source:<br>CTCAEv4.03<br>Gastrointestinal disorders:<br>Portal hypertension | 1: Not applicable<br>2: Decreased portal vein flow<br>3: Reversal/retrograde portal vein flow; associated with varices and/or ascites<br>4: Life-threatening consequences; urgent intervention indicated<br>5: Death | - Questionnaire and medical record validation<br>- Hepatic ultrasound with Doppler |
| Veno-occlusive disease of liver<br>(Sinusoidal obstructive syndrome) | Definition:<br>A syndrome characterized by at least three of five, otherwise unexplained, criteria: hepatomegaly; hyperbilirubinemia more than UNL; ascites; weight gain of at least 5%; and thrombocytopenia.[14]<br><br>Grading source:<br>St Jude modification of CTCAEv4.03<br>Hepatobiliary disorders:<br>Other, specify | 1: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated<br>2: Moderate; minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental ADL<br>3: Severe or medically significant but not immediately life threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self-care ADL<br>4: Life-threatening consequences; urgent intervention indicated<br>5: Death | - Questionnaire and medical record validation<br>- Weight<br>- Bilirubin, platelets<br>- Abdominal and hepatic ultrasound |

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| HEMATOLOGIC | | | |
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| **Health condition** | **Definition and Grading source** | **Grading** | **Data Grading source** |
| Anemia | Definition:<br>A disorder characterized by a reduction in the amount of hemoglobin in 100 ml of blood. Signs and symptoms of anemia may include pallor of the skin and mucous membranes, shortness of breath, palpitations of the heart, soft systolic murmurs, lethargy, and fatigability.<br><br>Grading source:<br>St Jude modification of CTCAEv4.03<br>Blood and lymphatic disorders: Anemia<br><br>ALL-STAR modification:<br>Units reported as SI-units (100 g/dL = 62 mmol/L) | 1: Hgb <LLN by sex/age-appropriate standards but >=10.0 g/dL (>=6.2 mmol/L)<br>2: Hgb <10.0 - 8.0 g/dL (<6.2 mmol/L–4.96 mmol/L)<br>3: Hgb <8.0 g/dL (< 4.96 mmol/L); transfusion indicated < 4.96 mmol/L<br>4: Life-threatening consequences; urgent intervention indicated<br>5: Death | - Questionnaire and medical record validation<br>- Hemoglobin |
| Coagulopathy | Definition:<br>Includes: disseminated intravascular coagulation, thrombotic thrombocytopenic purpura, hemolytic uremic syndrome, acquired von Willebrand disease, etc.<br><br>Grading source:<br>St Jude modification of CTCAEv4.03<br>Blood and lymphatic disorders: Disseminated intravascular Coagulation | 1: Not applicable<br>2: Not applicable<br>3: Laboratory findings and bleeding<br>4: Life-threatening consequences; urgent intervention indicated<br>5: Death | - Questionnaire and medical record validation<br>- Hematologic blood samples |

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| Iron overload | Definition:<br>Iron overload is defined as excess stores of iron in the body. Excess iron is deposited in organs throughout the body. The most notable organs with iron deposition are the liver, heart, and endocrine glands. Resulting symptoms and disease are related to specific organ damage.[15]<br><br>Grading source:<br>Category and grading according to St Jude<br><br>ALL-STAR modification:<br>Ferritin limit of 1000 ng/mL added to grade 2 since this value is often used as indicative of therapy in hematologic patients.[16] | 1: Tissue iron overload confirmed by imaging (e.g., T2*) or biopsy; intervention not indicated<br>2: Tissue iron overload confirmed by imaging (e.g., T2*) or biopsy; phlebotomy or oral chelation therapy indicated or initiated or ferritin > 1000 ng/mL<br>3: Tissue iron overload confirmed by imaging (e.g., T2*) or biopsy; intravenous or subcutaneous chelation therapy indicated or initiated<br>4: Life-threatening consequences; urgent intervention indicated or initiated; liver transplantation indicated or completed<br>5: Death | - Questionnaire and medical record validation<br>- Ferritin<br>- Cardiac MRI T2* |
| Neutropenia | Definition:<br>A finding based on laboratory test results that indicate a decrease in number of neutrophils in a blood specimen.<br><br>Grading source:<br>St Jude modification of CTCAEv4.03<br>Investigations:<br>Neutrophil count decreased<br><br>ALL-STAR modification:<br>Units reported as SI units. (1000 unit/mm3 = $1x10^{-9}$/L) | 1: <1500 - 1000/mm3 (<$1.5*10^{-9}$/L –$1*10^{-9}$/L)<br>2: <1000 - 500/mm3 (<$1*10^{-9}$/L –$0.5*10^{-9}$/L)<br>3: <500/mm3 (<$0.5*10^{-9}$/L)<br>4: Not applicable<br>5. Not applicable | - Questionnaire and medical record validation<br>- Neutrophil count |
| Polycythemia | Definition:<br>A finding based on laboratory test results that indicate increased levels of hemoglobin in a biological specimen<br><br>Grading source:<br>St Jude modification of CTCAEv4.03<br>Investigations:<br>Hemoglobin increased<br><br>ALL-STAR modification:<br>Units reported as SI units. (100 g/dL = 62mmol/L) | 1: Increase in >0 - 2 g/dL (>0–1.24 mmol/L) ULN or above baseline if baseline is above ULN<br>2: Increase in >2 - 4 g/dL (>1.24–2.48 mmol/L) above ULN or above baseline if baseline is above ULN; requiring phlebotomy or other medical intervention.<br>3: Increase in >4 g/dL (>2.48 mmol/L) above ULN or above baseline if baseline is above ULN<br>4: Not applicable<br>5. Not applicable | - Questionnaire and medical record validation<br>- Hemoglobin |

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| Thrombocytopenia | Definition:<br>Definition: A finding based on laboratory test results that indicate a decrease in number of platelets in a blood specimen.<br><br>Grading source:<br>CTCAEv4.03<br>Investigations:<br>Platelet count decreased<br><br>ALL-STAR modification:<br>Units reported as SI units. (1000 unit/mm3 = $1x10^{-9}$/L) | 1: Platelets <LLN - 75,000/mm3 ($75*10^{-9}$/L)<br>2: <75,000 - 50,000/mm3 ($<75–50*10^{-9}$/L)<br>3: <50,000 - 25,000/mm3 ($<50–25*10^{-9}$/L)<br>4: <25,000/mm3 ($<25*10^{-9}$/L)<br>5: Not applicable | - Questionnaire and medical record validation<br>- Platelet count |
| Thrombocytosis | Definition:<br>*Elevated number of platelets in the blood.*<br><br>Grading source:<br>St Jude modification of CTCAEv4.03<br>Blood and lymphatic disorders:<br>Other, specify | 1: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated<br>2: Moderate; minimal, local or non-invasive intervention indicated; limiting age appropriate instrumental ADL<br>**3:** Severe or medically significant but not immediately life threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self-care ADL<br>4: Life-threatening consequences; urgent intervention indicated<br>5: Death | - Questionnaire and medical record validation<br>- Platelet count |
| **IMMUNOLOGIC** | | | |
| **Health condition** | **Definition and Grading source** | **Grading** | **Data Grading source** |
| Autoimmune disorders | Definition:<br>A disorder resulting from loss of function or tissue destruction of an organ or multiple organs, arising from humoral or cellular immune responses of the individual to his own tissue constituents. (Includes: sarcoidosis, collagen vascular diseases -- rheumatoid arthritis, systemic lupus erythematosus, scleroderma, dermatomyositis, polyarteritis nodosa)<br><br>Grading source:<br>St Jude modification of CTCAEv4.03<br>Immune system disorders:<br>Autoimmune disorder | 1: Asymptomatic; serologic or other evidence of autoimmune reaction, with normal organ function; intervention not indicated<br>2: Evidence of autoimmune reaction involving a nonessential organ or function (e.g., hypothyroidism)<br>3: Autoimmune reactions involving major organ (e.g., colitis, anemia, myocarditis, kidney)<br>4: Life-threatening consequences; urgent intervention indicated<br>5: Death | - Questionnaire and medical record validation |

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| Graft-versus-host disease | Definition:<br>A complication of allogeneic hematopoietic stem cell transplantation involving inflammation, cell-mediated immunity, humoral immunity, and fibrosis and resulting in a syndrome of variable clinical features resembling autoimmune and other immunologic disorders.[17]<br><br>Grading source:<br>St Jude modification of CTCAEv4.03<br>Immune system disorders:<br>Other, specify | 1: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated or initiated<br>2: Moderate; minimal, local or non-invasive intervention indicated or initiated; limiting age appropriate instrumental ADL<br>3: Severe or medically significant but not immediately life threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self-care ADL<br>4: Life-threatening consequences; urgent intervention indicated<br>5: Death | - Questionnaire and medical record validation |
| Immunodeficiency | Definition:<br>Includes: hypogammaglobulinemia IgA deficiency, immunodeficiency NOT due to HIV or other infectious/neoplastic processes<br><br>Grading source:<br>St Jude modification of CTCAEv4.03<br>Immune system disorders:<br>Other, specify | 1: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated or initiated<br>2: Moderate; minimal, local or non-invasive intervention indicated (e.g. IVIG) or initiated; limiting age appropriate instrumental ADL<br>3: Severe or medically significant but not immediately life threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self-care ADL<br>4: Life-threatening consequences; urgent intervention indicated<br>5: Death | - Questionnaire and medical record validation<br>- Immunoglobulin levels |
| **INFECTIONS** | | | |
| **Health condition** | **Definition and Grading source** | **Grading** | |
| Bronchial/lung infections. Chronic and/or recurrent | Definition:<br>A disorder characterized by an infectious process involving the lungs. Defined as 3 infections in 6 months.<br><br>Grading source:<br>St Jude modification of CTCAEv4.03<br>Infections and infestations:<br>Lung infection | 1: Not applicable<br>2: Moderate symptoms; oral intervention indicated or initiated (e.g., antibiotic, antifungal, antiviral)<br>3: IV antibiotic, antifungal, or antiviral intervention indicated or initiated; invasive intervention indicated (e.g., radiologic, endoscopic, or operative intervention)<br>4: Life-threatening consequences; urgent intervention indicated<br>5: Death | - Questionnaire and medical record validation |
| Endocarditis infective | Definition:<br>A disorder characterized by an infectious process involving the endocardial layer of the heart.<br><br>Grading source:<br>St Jude modification of CTCAEv4.03<br>Infections and infestations:<br>Endocarditis infective | 1: Not applicable<br>2: Not applicable<br>3: IV antibiotic, antifungal, or antiviral intervention indicated or initiated; invasive intervention indicated (e.g., radiologic or operative intervention)<br>3: Life-threatening consequences; urgent intervention indicated<br>4: Death | - Questionnaire and medical record validation |

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| Gastrointestinal infection | Definition:<br>A disorder characterized by an infectious process involving the gastrointestinal tract. Includes: appendicitis diverticulitis, typhlitis, esophagitis, gastritis, and enterocolitis.<br><br>Grading source:<br>St Jude modification of CTCAEv4.03<br>Infections and infestations:<br>Small intestine infection | 1: Not applicable<br>2: Moderate symptoms; oral intervention indicated or initiated (e.g., antibiotic, antifungal, antiviral)<br>3: IV antibiotic, antifungal, or antiviral intervention indicated or initiated; invasive intervention indicated (e.g., radiologic, endoscopic, or operative intervention)<br>4: Life-threatening consequences; urgent intervention indicated<br>5: Death | - Questionnaire and medical record validation |
| Genitourinary infection | Definition:<br>A disorder characterized by an infectious process involving the urinary tract, most commonly the bladder and the urethra<br><br>Grading source:<br>St Jude modification of CTCAEv4.03<br>Infections and infestations:<br>Urinary tract infection | 1: Not applicable<br>2: Oral intervention indicated or initiated (e.g., oral or topical antibiotic, antifungal, antiviral)<br>3: IV antibiotic, antifungal, or antiviral intervention indicated or initiated; invasive intervention indicated (e.g., radiologic, endoscopic, or operative intervention)<br>4: Life-threatening consequences; urgent intervention indicated<br>5: Death | - Questionnaire and medical record validation<br>- Urine leucocytes and nitrite |
| Hepatitis B, chronic | Definition:<br>A disorder characterized by a viral pathologic process involving the liver parenchyma.<br><br>Grading source:<br>St Jude modification of CTCAEv4.03<br>Infections and infestations:<br>Hepatitis viral | 1: Asymptomatic<br>2: Asymptomatic but treated with antiviral therapy<br>3: Symptomatic liver dysfunction; fibrosis by biopsy; compensated cirrhosis; hospitalization or prolongation of existing hospitalization indicated<br>4: Decompensated liver function (e.g., coagulopathy, encephalopathy, coma, variceal hemorrhage)<br>5: Death | - Questionnaire and medical record validation<br>- HBV antibodies |
| Hepatitis C, chronic | Definition:<br>A disorder characterized by a viral pathologic process involving the liver parenchyma.<br><br>Grading source:<br>St Jude modification of CTCAEv4.03<br>Infections and infestations:<br>Hepatitis viral | 1: Asymptomatic<br>2: Asymptomatic but treated with antiviral therapy<br>3: Symptomatic liver dysfunction; fibrosis by biopsy; compensated cirrhosis; hospitalization or prolongation of existing hospitalization indicated<br>4: Decompensated liver function (e.g., coagulopathy, encephalopathy, coma, variceal hemorrhage)<br>5: Death | - Questionnaire and medical record validation<br>- HCV antibodies |

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| HIV infection | Definition:<br>*Infection with human immunodeficiency virus.*<br><br>Grading source:<br>St Jude modification of CTCAEv4.03<br>Infections and infestations:<br>Other, specify | 1: Asymptomatic or mild symptoms; clinical or diagnostic observations only<br>2: Moderate; minimal, local or noninvasive intervention indicated or initiated (e.g., HAART therapy); limiting age appropriate instrumental ADL<br>3: Severe or medically significant but not immediately life threatening, including sequelae of opportunistic infection; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self-care ADL<br>4: Life-threatening consequences; urgent intervention indicated<br>5: Death | - Questionnaire and medical record validation |
| Lymphatic infection | Definition:<br>A disorder characterized by an infectious process involving the lymph nodes<br><br>Grading source<br>St Jude modification of CTCAEv4.03<br>Infections and infestations:<br>Lymph gland infection | 1: Not applicable<br>2: Localized; local intervention indicated or initiated (e.g., topical antibiotic, antifungal, or antiviral)<br>3: IV antibiotic, antifungal, or antiviral intervention indicated or initiated; invasive intervention indicated (e.g., radiologic or operative intervention)<br>4: Life-threatening consequences; urgent intervention indicated<br>5: Death | - Questionnaire and medical record validation |
| Meningoencephalitis | Definition:<br>A disorder characterized by acute inflammation of the meninges of the brain and/or spinal cord.<br><br>Grading source:<br>St Jude modification of CTCAEv4.03<br>Infections and infestations:<br>Meningitis | 1: Not applicable<br>2: Not applicable<br>3: IV antibiotic, antifungal, or antiviral intervention indicated or initiated; invasive intervention indicated (e.g., radiologic or operative intervention); focal neurologic deficit<br>4: Life-threatening consequences; urgent intervention indicated<br>5: Death | - Questionnaire and medical record validation |
| Osteomyelitis | Definition:<br>A disorder characterized by an infectious process involving the bones.<br><br>Grading source:<br>St Jude modification of CTCAEv4.03<br>Infections and infestations:<br>Bone infection | 1: Not applicable<br>2: Not applicable<br>3: IV antibiotic, antifungal, or antiviral intervention indicated or initiated; invasive intervention indicated (e.g., radiologic or operative intervention)<br>4: Life-threatening consequences; urgent intervention indicated<br>5: Death | - Questionnaire and medical record validation |

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| Otitis media, chronic/recurrent | Definition:<br>A disorder characterized by an infectious process involving the middle ear. Defined as 3 infections in 6 months.<br><br>Grading source:<br>St Jude modification of CTCAEv4.03<br>Infections and infestations:<br>Otitis media | 1: Not applicable<br>2: Localized; local intervention indicated or initiated (e.g., topical antibiotic, antifungal, or antiviral)<br>3: IV antibiotic, antifungal, or antiviral intervention indicated or initiated; invasive intervention indicated (e.g., radiologic or operative intervention)<br>4: Life-threatening consequences; urgent intervention indicated<br>5: Death | - Questionnaire and medical record validation |
| Pelvic inflammatory disease | Definition:<br>A disorder characterized by an infectious process involving the pelvic cavity<br><br>Grading source:<br>St Jude modification of CTCAEv4.03<br>Infections and infestations:<br>Pelvic infection | 1: Not applicable<br>2: Moderate symptoms; oral intervention indicated or initiated (e.g., antibiotic, antifungal, antiviral)<br>3: IV antibiotic, antifungal, or antiviral intervention indicated or initiated; invasive intervention indicated (e.g., radiologic or operative intervention)<br>4: Life-threatening consequences; urgent intervention indicated<br>5: Death | - Questionnaire and medical record validation |
| Pharyngitis/tonsillitis, chronic/recurrent | Definition: A disorder characterized by inflammation of the throat. Defined as 3 infections in 6 months<br><br>Grading source:<br>St Jude modification of CTCAEv4.03<br>Infections and infestations:<br>Pharyngitis<br><br>ALL-STAR modification:<br>Includes also tonsillectomy due to recurring infections | 1: Not applicable<br>2: Localized; local intervention indicated or initiated (e.g., topical antibiotic, antifungal, or antiviral)<br>3: IV antibiotic, antifungal, or antiviral intervention indicated or initiated; invasive intervention indicated (e.g., radiologic, endoscopic, or operative intervention)<br>4: Life-threatening consequences; urgent intervention indicated<br>5: Death | - Questionnaire and medical record validation |
| Sinusitis, chronic/recurrent | Definition:<br>A disorder characterized by an infectious process involving the mucous membranes of the paranasal sinuses. Defined as 3 infections in 6 months.<br><br>Grading source:<br>St Jude modification of CTCAEv4.03<br>Infections and infestations:<br>Sinusitis<br><br>ALL-STAR modification:<br>Chronic is defined as lasting more than 12 weeks | 1: Not applicable<br>2: Localized; local intervention indicated or initiated (e.g., topical antibiotic, antifungal, or antiviral)<br>3: IV antibiotic, antifungal, or antiviral intervention indicated or initiated; invasive intervention indicated (e.g., radiologic, endoscopic, or operative intervention)<br>4: Life-threatening consequences; urgent intervention indicated<br>5: Death | - Questionnaire and medical record validation |

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| Soft tissue infection | Definition:<br>A disorder characterized by an infectious process involving soft tissues.<br><br>Grading source:<br>St Jude modification of CTCAEv4.03<br>Infections and infestations:<br>Soft tissue infection | 1: Not applicable<br>2: Moderate symptoms; oral intervention indicated or initiated (e.g., antibiotic, antifungal, antiviral)<br>3: IV antibiotic, antifungal, or antiviral intervention indicated or initiated; invasive intervention indicated (e.g., radiologic or operative intervention)<br>4: Life-threatening consequences; urgent intervention indicated<br>5: Death | - Questionnaire and medical record validation |
| **MUSCULOSKELETAL** | | | |
| **Health condition** | **Definition and Grading source** | **Grading** | **ALL-STAR data** |
| Amputation | Definition:<br>*Removal of a limb.*<br><br>Grading source:<br>Category and grading according to St Jude and<br><br>ICD-9-CM Diagnosis and Procedure Codes: Abbreviated and Full Code Titles. Centers for Medicare & Medicaid Services <https://www.cms.gov/medicare/coding/ICD9providerdiagnosticcodes/codes.html#><br><br>ALL-STAR modification: IDC-10 Version 2019. https://icd.who.int/browse10/2019/en> | 1: Partial ostectomy or other bone repair<br>2: Amputation below ankle or below elbow; revision of amputation<br>3: Total ostectomy; upper extremity amputation above elbow or higher; lower extremity amputation above ankle or higher<br>4: Not applicable<br>5: Not applicable | - Questionnaire and medical record validation |
| Arthralgia | Definition:<br>A disorder characterized by a sensation of marked discomfort in a joint<br><br>Grading source:<br>CTCAEv4.03<br>Musculoskeletal & connective tissue disorders:<br>Arthralgia | 1: Mild pain<br>2: Moderate pain; limiting instrumental ADL<br>3: Severe pain; limiting self-care ADL<br>4: Not applicable<br>5: Not applicable | - Questionnaire and medical record validation |
| Arthritis | Definition:<br>A disorder characterized by inflammation involving a joint.<br><br>Grading source:<br>CTCAEv4.03<br>Musculoskeletal & connective tissue disorders:<br>Arthritis | 1: Mild pain with inflammation, erythema, or joint swelling<br>2: Moderate pain associated with signs of inflammation, erythema, or joint swelling; limiting instrumental ADL<br>3: Severe pain associated with signs of inflammation, erythema, or joint swelling; irreversible joint damage; disabling; limiting self-care ADL<br>4: Not applicable<br>5: Not applicable | - Questionnaire and medical record validation |

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| Bone mineral density deficit | Definition:<br>A disorder characterized by reduced bone mass, with a decrease in cortical thickness and in the number and size of the trabeculae of cancellous bone (but normal chemical composition), resulting in increased fracture incidence.<br><br>Grading source<br>St Jude modification of CTCAEv4.03<br>Musculoskeletal & connective tissue disorders:<br>Osteoporosis<br><br>-and-<br><br>New Grading source (Pediatric)<br>International Society of Clinical Densitometry | Adults<br>1: Radiologic evidence of osteoporosis or Bone Mineral Density (BMD) t-score -1 to -2.5 (osteopenia); no loss of height or intervention indicated;<br>2: BMD t-score <-2.5; loss of height <2 cm; anti-osteoporotic therapy indicated or initiated; therapy to improve BMD indicated or initiated; limiting instrumental ADL;<br>3: Loss of height >=2 cm; hospitalization indicated; limiting self-care ADL<br>4: Not applicable<br>5: Not applicable | Pediatric<br>1: Radiologic evidence of low BMD with z score of ≤-2.0 and no history of significant fractures<br>2: Low BMD (z-score ≤-2.0) and significant fracture history (defined as a long bone fracture of the lower extremity, vertebral compression, 2 or more long bone fracture of the upper extremities); therapy to improve BMD indicated or initiated<br>3: Limiting self-care ADL<br>4: Not applicable<br>5: Not applicable | - Questionnaire and medical record validation<br>- DXA bone scan |
| Hernia | Definition:<br>Includes: abdominal, umbilical, ventral, inguinal, femoral, etc.<br><br>Grading source:<br>St Jude modification of CTCAEv4.03<br>Musculoskeletal & connective tissue disorders:<br>Other, specify | 1: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated<br>2: Moderate; minimal, local or non-invasive intervention indicated; limiting age appropriate instrumental ADL<br>3: Severe or medically significant but not immediately life threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self-care ADL<br>4: Life-threatening consequences; urgent intervention indicated<br>5: Death | | - Questionnaire and medical record validation |
| Intervertebral disc disorder | Definition:<br>Includes: disc degeneration, disc herniation<br><br>Grading source:<br>St Jude modification of CTCAEv4.03<br>Musculoskeletal & connective tissue disorders:<br>Other, specify | 1: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated<br>2: Moderate; minimal, local or non-invasive intervention indicated; limiting age appropriate instrumental ADL<br>3: Severe or medically significant but not immediately life threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self -care ADL<br>4: Life-threatening consequences; urgent intervention indicated<br>5: Death | | - Questionnaire and medical record validation |

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| Kyphosis | Definition:<br>A disorder characterized by an abnormal increase in the curvature of the thoracic portion of the spine.<br><br>Grading source<br>St Jude modification of CTCAEv4.03<br>Musculoskeletal & connective tissue disorders:<br>Kyphosis | 1: Not applicable<br>2: Moderate accentuation; limiting instrumental ADL<br>3: Severe accentuation; operative intervention indicated; limiting self-care ADL<br>4: Not applicable<br>5: Not applicable | - Questionnaire and medical record validation |
| Limb length discrepancy | Definition:<br>A disorder characterized by of a discrepancy between the lengths of the lower or upper extremities<br><br>Grading source:<br>St Jude modification of CTCAEv4.03<br>Musculoskeletal & connective tissue disorders:<br>Unequal limb length | 1: Not applicable<br>2: Moderate length discrepancy 2-5 cm; shoe lift indicated; limiting instrumental ADL<br>3: Severe length discrepancy >5 cm; limiting self-care ADL; disabling; operative intervention indicated<br>4: Not applicable<br>5: Not applicable | - Questionnaire and medical record validation |
| Osteonecrosis | Definition:<br>A disorder characterized by necrotic changes in the bone tissue due to interruption of blood supply. Most often affecting the epiphysis of the long bones, the necrotic changes result in the collapse and the destruction of the bone structure.<br><br>Grading source:<br>St Jude modification of CTCAEv4.03<br>Musculoskeletal & connective tissue disorders:<br>Avascular necrosis | 1: Asymptomatic; clinical or diagnostic observations only; intervention not indicated<br>2: Symptomatic; medical intervention indicated (e.g., analgesics, anti-inflammatory); limiting instrumental ADL<br>3: Severe symptoms; limiting self-care ADL; elective operative intervention indicated<br>4: Life-threatening consequences; urgent intervention indicated<br>5: Death | - Questionnaire and medical record validation |
| Palatal defects, acquired | Definition:<br>*Palatal defect not present at birth*<br><br>Grading source:<br>St Jude modification of CTCAEv4.03<br>Musculoskeletal & connective tissue disorders:<br>Other, specify | 1: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated<br>2: Moderate; minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental ADL<br>3: Severe or medically significant but not immediately life threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self-care ADL<br>4: Life-threatening consequences; urgent intervention indicated<br>5: Death | - Questionnaire and medical record validation |

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| Scoliosis | Definition:<br>A disorder characterized by a malformed, lateral curvature of the spine.<br><br>Grading source:<br>St Jude modification of CTCAEv4.03<br>Musculoskeletal & connective tissue disorders:<br>Scoliosis | 1: > 8 and <15 degrees; clinically undetectable<br>2: >=15 - 30 degrees; visible by forward flexion; limiting instrumental ADL<br>3: >=30 degrees; scapular prominence in forward flexion; operative intervention indicated; limiting self-care ADL; disabling<br>4: Not applicable<br>5: Not applicable | - Questionnaire and medical record validation |
| Skeletal spine disorder | Definition:<br>Includes: spondylitis, spondylolisthesis, spondylomalacia, spondydylosis<br><br>Grading source:<br>St Jude modification of CTCAEv4.03<br>Musculoskeletal & connective tissue disorders:<br>Other, specify | 1: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated<br>2: Moderate; minimal, local or non-invasive intervention indicated; limiting age appropriate instrumental ADL<br>3: Severe or medically significant but not immediately life threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self-care ADL<br>4: Life-threatening consequences; urgent intervention indicated<br>5: Death | - Questionnaire and medical record validation |
| Slipped capital femoral epiphysis | Definition:<br>Posterior and inferior displacement of the femoral epiphysis relative to the femoral head and neck.[18]<br><br>Grading source:<br>St Jude modification of CTCAEv4.03<br>Musculoskeletal & connective tissue disorders:<br>Other, specify | 1: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated<br>2: Moderate; minimal, local or non-invasive intervention indicated; limiting age appropriate instrumental ADL<br>3: Severe or medically significant but not immediately life threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self-care ADL<br>4: Life-threatening consequences; urgent intervention indicated<br>5: Death | - Questionnaire and medical record validation |
| **ORAL-DENTAL** | | | |
| **Health condition** | **Definition and Grading source** | **Grading** | **ALL-STAR data** |
| Dental caries | Definition:<br>A biofilm-mediated, sugar-driven, multifactorial disease that results in the phasic demineralization and remineralization of dental hard tissues.[19]<br><br>Grading source:<br>ALL-STAR research team.<br>Decayed Missed Filled (DMF)-teeth/surfaces scoring system and International Caries Detection and Assessment System (ICDAS).[19] | 1: No clinical visible carious lesions.<br>2: Initial caries, non-cavitated (may be white, yellow/brown); dental intervention needed including preventive measures.<br>3: Carious lesion in enamel with cavity; dental restoration needed.<br>4: Shadow from dentin with or without localized enamel breakdown; dental treatment needed.<br>5: Distinct and extensive distinct cavity with visible dentine; dental restoration, and/or endodontic treatment, or extraction; disabling. | - Questionnaire and medical record validation<br>- Dental evaluation |

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| Dental erosion | Definition:<br>A condition characterized by loss or wear of dental hard tissue by acids and not caused by bacteria.<br>May be caused by intrinsic (e.g., acid reflux and excessive vomiting) and/or extrinsic (e.g., diet) factors.[20]<br><br>Grading source:<br>ALL-STAR research team.<br>Basic Erosive Wear Examination (BEWE)-score.[21] | 1: No surface loss<br>2: Initial loss of enamel surface texture<br>3: Distinct defect, hard tissue loss (dentine) less than 50% of the surface area<br>4: Hard tissue loss more than 50% of the surface area. Disabling.<br>5: Not applicable. | - Questionnaire and medical record validation<br>- Dental evaluation |
| Gingivitis | Definition:<br>Inflammation of the gums includes gingival redness, edema, bleeding on slight provocation or spontaneously, and swelling with loss of stippling. Difficulty in chewing. Gingivitis can lead to periodontitis.[22–24]<br><br>Grading source:<br>ALL-STAR research team.<br>Plaque index and gingival index.[22,23] | 1: No plaque, No inflammation<br>2: A film of plaque adhering to the free gingival margin and adjacent area of the tooth. Mild inflammation.<br>3: Moderate accumulation of soft deposits within the gingival pocket, or the tooth and gingival margin, which can be seen with the naked eye. Moderate inflammation with bleeding on probing.<br>4: Abundance of soft matter within the gingival pocket and/or on the tooth and gingival margin.Severe inflammation and tendency to spontaneous bleeding. Dental intervention needed.<br>5: Not applicable. | - Questionnaire and medical record validation<br>- Dental evaluation |
| Periodontitis | Definition:<br>A chronic multifactorial inflammatory disease associated with dysbiotic plaque biofilms and characterized by progressive destruction of the tooth-supporting apparatus. Its primary features include the loss of periodontal tissue support, manifested through clinical attachment loss (CAL) and radiographically assessed alveolar bone loss, presence of periodontal pocketing and gingival bleeding.[25]<br><br>Grading source:<br>ALL-STAR research team.<br>Plaque index, gingival index, periodontal pocket depth assessment.[22,23,25] | 1: Mild to moderate periodontitis<br>2: Moderate to severe periodontitis<br>Based on bleeding on<br>probing scores and probing pocket depths > 5 mm etc.<br>3: Tooth loss due to periodontitis<br>4: All stages require dental intervention, from preventive measure to oral rehabilitation.<br>5: Not applicable. | - Questionnaire and medical record validation<br>- Dental/periodontal evaluation |

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| Acute sialadenitis | Definition:<br>Acute inflammation of salivary glands, usually the major ones, and most commonly the parotid gland, followed by submandibular and sublingual glands. May be induced by infection, medication autoimmune or metabolic disease.[26]<br><br>Grading source:<br>ALL-STAR research team | 1: Not applicable<br>2: Painful swelling<br>reddened skin, edema of the cheek and neck; medical intervention indicated.<br>3: Low-grade fever, malaise, elevated ESR, CRP, leukocytosis, purulent exudate from duct orifice; urgent intervention indicated.<br>4: Life-threatening consequences; urgent intervention indicated.<br>5: Not applicable | - Questionnaire and medical record validation<br>- Orofacial evaluation including inspection and palpation, sialometry |
| Chronic sialadenitis | Definition<br>Chronic inflammation of salivary glands, usually the major ones, and most commonly the parotid gland, followed by submandibular and sublingual glands. May be induced by infection, medication autoimmune or metabolic disease.[26]<br><br>Grading source:<br>ALL-STAR research team | 1: Mild pain and swelling.<br>2: Moderate pain and swelling/recurrent swellings, related to meals, often unilateral<br>3: reddened duct orifice and decreased salivary flow.<br>4: Severe pain and secondary infection; medical intervention indicated.<br>5: Not applicable. | - Questionnaire and medical record validation<br>- Orofacial evaluation including inspection and palpation, sialometry |
| Salivary gland dysfunction | Definition:<br>A condition characterized by changes in salivary flow, amount, and/or quality of saliva produced. Most commonly hyposalivation and xerostomia.[27]<br><br>Grading source:<br>ALL-STAR research team.<br>Measurement of whole saliva flow rates (sialometry); Xerostomia Inventory (XI); Visual Analogue Scale; Clinical Oral Dryness Score (CODS).[28] | 1: Mild symptoms of xerostomia; normal unstimulated (UWS, 0.3-0.5 ml/min) and chewing-stimulated whole saliva (SWS, 1-3 ml/min) flow rates.<br>2: Mild-moderate symptoms and low secretors (UWS 0.2 ml/min).<br>3: Severe symptoms and hyposalivation (UWS ≤ 0.1 ml/min, and SWS ≤ 0.70 ml/min).<br>4: Persistent hyposalivation with clinical consequences including dental caries, dental erosion, gingivitis, mucosal ulcerations and infections, difficulties chewing, swallowing, taste and speech etc.; dental and medical intervention; impact on food intake; disabling.<br>5: Not applicable. | - Questionnaire and medical record validation<br>- Clinical oral examination, sialometry |

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| Temporomandibular joint disorder | Definition:<br>Collection of conditions characterized by pain in the jaw muscles and/ or temporomandibular joint (TMJ) as well as surrounding structures, functional limitations in the TMJ or sounds (cracking, crepitation) from the TMJ. May be transient, recurrent or chronic.[29]<br><br>Grading source:<br>ALL-STAR research team.<br>Assessment of jaw muscles (palpation of the temporalis and masseter muscles) and joint pain (palpation and upon function); jaw movements (i.e., opening, lateral, and protrusive), functional and morphological dental occlusion.[29] | 1: Mild orofacial pain/TMD myalgia and or arthralgia.<br>2: Moderate orofacial pain/TMD myalgia and/or arthralgia.<br>3: Severe orofacial pain/TMD myalgia and/or arthralgia; medical and dental intervention needed.<br>4: Extensive TMD; may require surgical intervention.<br>5: Not applicable. | - Questionnaire and medical record validation<br>- Orofacial and dental evaluation |
| Dental maldevelopment | Definition:<br>A disorder characterized by pathological processes of the teeth occurring during tooth development. Includes: adontia, hypodontia, microdontia, root stunting, enamel demineralization/ decalcification etc.<br><br>Grading source:<br>CTCAEv4.03<br>Gastrointestinal disorders:<br>Tooth development disorder | 1: Asymptomatic; hypoplasia of teeth or enamel.<br>2: Impairment correctable with oral surgery.<br>3: Malformation with impairment not surgically correctable; disabling.<br>3: Not applicable.<br>4: Not applicable. | - Questionnaire and medical record validation<br>- Orofacial and dental evaluation |
| **NEUROLOGIC** | | | |
| **Health condition** | **Definition and Grading source** | **Grading** | **ALL-STAR data** |
| Autonomic dysfunction | Definition:<br>Disorder in the autonomic nerve system. Includes Horner's syndrome<br><br>Grading source:<br>St Jude modification of CTCAEv4.03<br>Nervous system disorders:<br>Other, specify | 1: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated<br>2: Moderate; minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental ADL<br>3: Severe or medically significant but not immediately life threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self-care ADL<br>4: Life-threatening consequences; urgent intervention indicated<br>5: Death | - Questionnaire, COMPASS31, and medical record validation<br>- Heart rate variability |

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| Cavernoma | Definition:<br>*A cluster of abnormal blood vessels usually found in the brain or spinal cord.*<br><br>Grading source:<br>CTCAEv4.03<br>Nervous system disorders:<br>Other, specify | 1: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated<br>2: Moderate; minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental ADL<br>3: Severe or medically significant but not immediately life threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self-care ADL<br>4: Life-threatening consequences; urgent intervention indicated<br>5: Death | - Questionnaire and medical record validation |
| Cerebellar dysfunction | Definition:<br>A disorder characterized by lack of coordination of muscle movements resulting in the impairment or inability to perform voluntary activities. Includes: demyelization, drug-induced, hereditary, nutritional, surgical, trauma, tumors, or vascular causes.<br><br>Grading source:<br>St Jude modification of CTCAEv4.03<br>Nervous system disorders:<br>Ataxia | 1: Asymptomatic; clinical or diagnostic observations only; intervention not indicated<br>2: Moderate symptoms; limiting instrumental ADL<br>3: Severe symptoms; limiting self-care ADL; mechanical assistance indicated<br>4 Not applicable<br>5: Not applicable | - Questionnaire and medical record validation |
| Cerebral necrosis | Definition:<br>A disorder characterized by a necrotic process occurring in the brain and/or spinal cord.<br><br>Grading source:<br>St Jude modification of CTCAEv4.03<br>Nervous system disorders:<br>Central nervous system necrosis | 1: Asymptomatic; clinical or diagnostic observations only; intervention not indicated<br>2: Moderate symptoms; corticosteroids indicated<br>3: Severe symptoms; medical intervention indicated (e.g., hyperbaric treatment of brain radiation necrosis)<br>4: Life-threatening consequences; urgent/surgical intervention indicated<br>5: Death | - Questionnaire and medical record validation |
| Cerebrovascular accident | Definition:<br>A disorder characterized by a sudden loss of sensory function due to an intracranial vascular event. Includes: lacunes, hemorrhagic stroke, Ischemic stroke.<br><br>Grading source:<br>St Jude modification of CTCAEv4.03<br>Nervous system disorders:<br>Stroke | 1: Asymptomatic or mild neurologic deficit; radiographic findings only<br>2: Moderate neurologic deficit<br>3: Severe neurologic deficit<br>4: Life-threatening consequences; urgent intervention indicated<br>5: Death | - Questionnaire and medical record validation |

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| Cerebrovascular disease | Definition:<br>Includes: stenotic or occlusive large vessel disease, moyamoya.<br><br>Grading source:<br>St Jude modification of CTCAEv4.03<br>Nervous system disorders:<br>Other, specify | 1: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated<br>2: Moderate; minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental ADL<br>3: Severe or medically significant but not immediately life threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self-care ADL<br>4: Life-threatening consequences; urgent intervention indicated<br>5: Death | - Questionnaire and medical record validation |
| Cranial nerve disorder | Definition:<br>A disorder characterized by involvement of a cranial nerve<br><br>Grading source:<br>St Jude modification of CTCAEv4.03<br>Nervous system disorders:<br>Trigeminal, oculomotor, etc. Cranial nerve disorder | 1: Asymptomatic; clinical or diagnostic observations only; intervention not indicated<br>2: Moderate symptoms; limiting instrumental ADL<br>3: Severe symptoms; limiting self-care ADL (e.g., surgical intervention indicated)<br>4: Not applicable<br>5: Not applicable | - Questionnaire and medical record validation |
| Dysarthria | Definition:<br>A disorder characterized by slow and slurred speech resulting from an inability to coordinate the muscles used in speech.<br><br>Grading source:<br>St Jude modification of CTCAEv4.03<br>Nervous system disorders:<br>Dysarthria | 1: Mild slurred speech (easily understood)<br>2: Moderate impairment of articulation or slurred speech (some need for repetition to be understood)<br>3: Severe impairment of articulation or slurred speech (unintelligible speech)<br>4: Not applicable<br>5: Not applicable | - Questionnaire and medical record validation |
| Generalized muscle weakness | Definition:<br>A disorder characterized by a reduction in the strength of muscles in multiple anatomic sites<br><br>Grading source:<br>ALL-STAR modification of CTCAEv4.03<br>Musculoskeletal and connective tissue disorders | 1: Symptomatic; weakness perceived by patient but not evident on physical exam<br>2: Symptomatic; weakness evident on physical exam; weakness limiting instrumental ADL<br>3: Weakness limiting self-care ADL; disabling; more than 2 SD below the expected mean (based on ALL-STAR control values)<br>4: Not applicable<br>5: Not applicable | - Questionnaire and medical record validation<br>- Physical tests |

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| Headaches, chronic/ recurrent | Definition:<br>Includes: migraines<br>Chronic headaches defined as headaches 15 days in a month for 3 consecutive months<br>Recurrent headaches defined as at least 5 headaches over lifetime<br><br>Grading source:<br>St Jude modification of CTCAEv4.03<br>Nervous system disorders:<br>Headaches<br><br>ALL-STAR modification: chronic/recurring headache is defined as more than one episode per week. Migraine included as diagnose independent of frequency. | 1: Mild pain<br>2: Moderate pain requiring prescriptive abortive medication; limiting instrumental ADL<br>3: Severe pain requiring prophylactic medication; limiting self-care ADL<br>4: Not applicable<br>5: Not applicable | - Questionnaire and medical record validation |
| Hydrocephalus | Definition:<br>A disorder characterized by an abnormal increase of cerebrospinal fluid in the ventricles of the brain.<br><br>Grading source:<br>CTCAEv4.03<br>Nervous system disorders:<br>Hydrocephalus | 1: Asymptomatic; clinical or diagnostic observations only; intervention not indicated<br>2: Moderate symptoms; intervention not indicated<br>3: Severe symptoms or neurological deficit; intervention indicated<br>4: Life-threatening consequences; urgent intervention indicated<br>5: Death | - Questionnaire and medical record validation |
| Hydrosyringomyelia | Definition: -<br>Includes: syrinx, syringohydromyelia, syringomyelia<br><br>Grading source:<br>St Jude modification of CTCAEv4.03<br>Nervous system disorders:<br>Other, specify | 1: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated<br>2: Moderate; minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental ADL<br>3: Severe or medically significant but not immediately life threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self-care ADL<br>4: Life-threatening consequences; urgent intervention indicated<br>5: Death | - Questionnaire and medical record validation |
| Intracranial hemorrhage | Definition:<br>A disorder characterized by bleeding from the cranium.<br>Includes: subdural, subarachnoid, intraventricular.<br><br>Grading source:<br>St Jude modification of CTCAEv4.03<br>Nervous system disorders:<br>Intracranial hemorrhage | 1: Asymptomatic; clinical or diagnostic observations only; intervention not indicated (MRI evidence of microhemorrhage, e.g. hemosiderin)<br>2: Moderate symptoms; medical intervention indicated<br>3: Ventriculostomy, ICP monitoring, intraventricular thrombolysis, or operative intervention indicated<br>4: Life-threatening consequences; urgent intervention indicated<br>5: Death | - Questionnaire and medical record validation |

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| Movement disorders | Definition:<br>A disorder characterized by uncontrolled and purposeless movements. Includes: athetosis, ballism, chorea, dystonia, myoclonus, opsoclonus/ myoclonus, Parkinsonism, restless legs, tic tremor, torticollis.<br><br>Grading source:<br>St Jude modification of CTCAEv4.03<br>Nervous system disorders:<br>Movements involuntary | 1: Mild involuntary movements<br>2: Moderate involuntary movements; limiting instrumental ADL<br>3: Severe involuntary movements; limiting self-care ADL<br>4: Not applicable<br>5: Not applicable | - Questionnaire and medical record validation |
| Multiple sclerosis | Definition:<br>An inflammatory disorder of the brain and spinal cord.[30]<br><br>Grading source:<br>St Jude modification of CTCAEv4.03<br>Nervous system disorders:<br>Other, specify | 1: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated<br>2: Moderate; minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental ADL<br>3: Severe or medically significant but not immediately life threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self-care ADL<br>4: Life-threatening consequences; urgent intervention indicated<br>5: Death | - Questionnaire and medical record validation |
| Narcolepsy | Definition:<br>A disorder characterized by characterized by excessive sleepiness during the daytime<br><br>Grading source:<br>St Jude modification of CTCAEv4.03<br>Nervous system disorders:<br>Hypersomnia | 1: Not applicable<br>2: Documentation of narcolepsy without need for therapy; moderate increased need for sleep<br>3: Documentation of narcolepsy with need for therapy; severe increased need for sleep<br>4: Not applicable<br>5: Not applicable | - Questionnaire and medical record validation |
| Nerve root disorder | Definition:<br>A disorder characterized by inflammation involving a nerve root. Patients experience marked discomfort radiating along a nerve path because of spinal pressure on the connecting nerve root. Includes: radiculopathy, plexopathy, cauda equina syndrome.<br><br>Grading source:<br>St Jude modification of CTCAEv4.03<br>Nervous system disorders:<br>Radiculitis | 1: Mild symptoms<br>2: Moderate symptoms; limiting instrumental ADL; medical intervention indicated<br>3: Severe symptoms; limiting self-care ADL<br>4: Life-threatening consequences; urgent intervention indicated<br>5: Death | - Questionnaire and medical record validation |

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| Neurogenic bladder | Definition:<br>Dysfunction of the lower urinary tract characterized by damage to the central nervous system (CNS), autonomic nervous system (ANS), or peripheral nervous system (PNS).[31]<br><br>Grading source:<br>St Jude modification of CTCAEv4.03<br>Nervous system disorders:<br>Other, specify | 1: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated<br>2: Moderate; minimal, local or noninvasive intervention indicated (medical management e.g., oxybutynin); limiting age appropriate instrumental ADL<br>3: Severe or medically significant but not immediately life threatening; hospitalization or prolongation of existing hospitalization indicated; surgical intervention indicated (e.g. ileal-anal pouch); disabling; limiting self-care ADL<br>4: Life-threatening consequences; urgent intervention indicated<br>5: Death | - Questionnaire, COMPASS31, and medical record validation |
| Neurogenic bowel | Definition:<br>Dysfunction of the bowel characterized by damage to the central nervous system (CNS), autonomic nervous system (ANS), or peripheral nervous system (PNS).[32]<br><br>Grading source:<br>St Jude modification of CTCAEv4.03<br>Nervous system disorders:<br>Other, specify | 1: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated<br>2: Moderate; minimal, local or noninvasive intervention indicated (e.g. stool softener); limiting age appropriate instrumental ADL<br>3: Severe or medically significant but not immediately life threatening; hospitalization or prolongation of existing hospitalization indicated; surgical intervention indicated (e.g. MACE); disabling; limiting self-care ADL<br>4: Life-threatening consequences; urgent intervention indicated<br>5: Death | - Questionnaire and medical record validation |
| Neuromuscular disorders | Definition:<br>Includes: dermatomyositis, myotonia, neuromuscular disorder, polymyositis, rhabdomyolysis, steroid myopathy, critical illness myopathy/neuropathy<br><br>Grading source:<br>St Jude modification of CTCAEv4.03<br>Nervous system disorders:<br>Other, specify | 1: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated<br>2: Moderate; minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental ADL<br>3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self-care ADL<br>4: Life-threatening consequences; urgent intervention indicated<br>5: Death | - Questionnaire and medical record validation |
| Paralytic disorder | Definition:<br>Includes: hemiparesis/ plegia, quadriparesis/ plegia, parapareis/ plegia, flaccid paralysis, spastic paralysis<br><br>Grading source:<br>St Jude modification of CTCAEv4.03<br>Nervous system disorders:<br>Other, specify | 1: Asymptomatic or mild symptoms (e.g., facial paraparesis); clinical or diagnostic observations only; intervention not indicated<br>2: Moderate (e.g., paraparesis); minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental ADL<br>3: Severe weakness or sensory loss (e.g., paraplegia requiring wheelchair); limiting self-care ADL<br>4: Life-threatening consequences (e.g., quadriplegia); urgent intervention indicated<br>5: Death | - Questionnaire and medical record validation |

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| Peripheral motor neuropathy | Definition:<br>A disorder characterized by inflammation or degeneration of the peripheral motor nerves.<br>Includes: inflammatory demyelinating polyneuropathy disorder - Guillain-Barre syndrome.<br><br>Grading source:<br>CTCAEv4.03<br>Nervous system disorders:<br>Peripheral motor neuropathy | 1: Asymptomatic; clinical or diagnostic observations only; intervention not indicated<br>2: Moderate symptoms; limiting instrumental ADL<br>3: Severe symptoms; limiting self- care ADL; assistive device indicated<br>4: Life-threatening consequences; urgent intervention indicated<br>5: Death | - Questionnaire and medical record validation<br>- Neurological evaluation according to TNS including electroneurography. |
| Peripheral sensory neuropathy | Definition:<br>A disorder characterized by inflammation or degeneration of the peripheral sensory nerves.<br><br>Grading source:<br>CTCAEv4.03<br>Nervous system disorders:<br>Peripheral sensory neuropathy | 1: Asymptomatic; loss of deep tendon reflexes or paresthesia<br>2: Moderate symptoms; limiting instrumental ADL<br>3: Severe symptoms; limiting self-care ADL<br>4: Life-threatening consequences; urgent intervention indicated<br>5: Death | - Questionnaire and medical record validation<br>- Neurological evaluation according to TNS including electroneurography. |
| Pseudomeningocele | Definition:<br>An accumulation of cerebrospinal fluid in the extradural space due to a fault in the dural arachnoid layer.[33]<br><br>Grading source:<br>ST Jude modification of CTCAEv4.03<br>Nervous system disorders:<br>Other, specify | 1: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated<br>2: Moderate; minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental ADL<br>3: Severe or medically significant but not immediately life threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self-care ADL<br>4: Life-threatening consequences; urgent intervention indicated<br>5: Death | - Questionnaire and medical record validation |
| Pseudotumor cerebri | Definition:<br>A syndrome with increased intracranial pressure without a space-occupying lesion.[34]<br><br>Grading source:<br>ST Jude modification of CTCAEv4.03<br>Nervous system disorders:<br>Other, specify | 1: Asymptomatic or mild symptoms; clinical management or diagnostic observations only (e.g., weight control)<br>2: Moderate; minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental ADL; medical intervention indicated or initiated (e.g., acetazolamide)<br>3: Severe or medically significant but not immediately life threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self-care ADL; surgical intervention indicated or initiated (e.g., lumbar puncture)<br>4: Life-threatening consequences; urgent intervention indicated (e.g., severe visual impairment)<br>5: Death | - Questionnaire and medical record validation |

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| Seizures | Definition:<br>A transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain.[35]<br><br>Grading source:<br>St Jude category and grading according to multidisciplinary team consensus | 1: Seizures not requiring medication<br>2: Seizures requiring one non-prn medication<br>3: Seizures requiring two or more non-prn medications; poorly controlled seizures with prescribed medications<br>4: Seizures requiring evaluation for surgical intervention<br>5: Death | - Questionnaire and medical record validation |
| **OCULAR/VISUAL** | | | |
| **Health condition** | **Definition and Grading source** | **Grading** | **ALL-STAR data** |
| Cataract | Definition:<br>A disorder characterized by partial or complete opacity of the crystalline lens of one or both eyes. This results in a decrease in visual acuity and eventual blindness if untreated.<br><br>Grading source:<br>St Jude modification of CTCAEv4.03<br>Eye disorders:<br>Cataract | 1: Asymptomatic; clinical or diagnostic observations only; intervention not indicated (20/30 or better)<br>2: Symptomatic; moderate decrease in visual acuity (20/40 or better)<br>3: Symptomatic with marked decrease in visual acuity (worse than 20/40 but better than 20/200); operative intervention indicated (e.g., cataract surgery)<br>4: Blindness (20/200 or worse) in the affected eye<br>5: Not applicable | - Questionnaire and medical record validation |
| Diplopia | Definition:<br>*Double vision*<br><br>Grading source:<br>St Jude modification of CTCAEv4.03<br>Eye disorders:<br>Other, specify | 1: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated<br>2: Moderate; minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental ADL<br>3: Severe or medically significant but not immediately sight threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self-care ADL<br>4: Not applicable<br>5: Not applicable | - Questionnaire and medical record validation |
| Dry eye syndrome | Definition:<br>Includes: Keratitis sicca, xerophthalmia, kerato-conjunctivitis sicca, Sjogren's syndrome, lacrimal duct atrophy, limbal stem cell deficiency.<br><br>Grading source:<br>St Jude modification of CTCAEv4.03<br>Eye disorders:<br>Other, specify | 1: Asymptomatic; clinical or diagnostic observations only; mild symptoms relieved by lubricants<br>2: Symptomatic; multiple agents indicated; limiting instrumental ADL<br>3: Decrease in visual acuity (<20/40); limiting self-care ADL<br>4: Not applicable<br>5: Not applicable | - Questionnaire, COMPASS31 and medical record validation |

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| Eyelid function disorder | Definition:<br>Includes: entropion, ectropion, lagophthalmos, ptosis<br><br>Grading source:<br>St Jude modification of CTCAEv4.03<br>Eye disorders:<br>Other, specify | 1: Asymptomatic; clinical or diagnostic observations only; intervention not indicated<br>2: Symptomatic; non-operative intervention indicated; limiting instrumental ADL<br>3: Limiting self-care ADL; operative intervention indicated<br>4: Not applicable<br>5: Not applicable | - Questionnaire and medical record validation |
| Glaucoma | Definition:<br>A disorder characterized by an increase in pressure in the eyeball due to obstruction of the aqueous humor outflow<br><br>Grading source:<br>CTCAEv4.03<br>Eye disorders:<br>Glaucoma | 1: Elevated intraocular pressure (EIOP) with single topical agent for intervention; no visual field deficit<br>2: EIOP causing early visual field deficits; multiple topical or oral agents indicated; limiting instrumental ADL<br>3: EIOP causing marked visual field deficits (e.g., involving both superior and inferior visual fields); operative intervention indicated; limiting self-care ADL<br>4: Blindness (20/200 or worse) in the affected eye<br>5: Not applicable | - Questionnaire and medical record validation |
| Ocular disease, noninfectious | Definition:<br>Includes: chorioretinitis, uveitis, iritis, scleritis<br><br>Grading source:<br>St Jude modification of CTCAEv4.03<br>Eye disorders:<br>Other, specify | 1: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated<br>2: Moderate; minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental ADL<br>3: Severe or medically significant but not immediately sight threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self-care ADL<br>4: Sight-threatening consequences; urgent intervention indicated; blindness (20/200 or worse) in the affected eye<br>5: Not applicable | - Questionnaire and medical record validation |
| Ocular surface disease | Definition:<br>A disorder characterized by inflammation to the cornea of the eye<br><br>Grading source:<br>St Jude modification of CTCAEv4.03<br>Eye disorders:<br>Keratitis | 1: Not applicable<br>2: Symptomatic; medical intervention indicated (e.g., topical agents); limiting instrumental ADL<br>3: Decline in vision (worse than 20/40 but better than 20/200); limiting self-care ADL<br>4: Perforation or blindness (20/200 or worse) in the affected eye<br>5: Not applicable | - Questionnaire and medical record validation |
| Photophobia | Definition:<br>A disorder characterized by fear and avoidance of light.<br><br>Grading source:<br>CTCAEv4.03<br>Eye disorders:<br>Photophobia | 1: Symptomatic but not limiting ADL<br>2: Limiting instrumental ADL<br>3: Limiting self-care ADL<br>4: Not applicable<br>5: Not applicable | - Questionnaire, COMPASS31 and medical record validation |

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| Phthisis bulbi | Definition:<br>Blind, painful eye<br><br>Grading source:<br>St Jude modification of CTCAEv4.03<br>Eye disorders<br>Eye pain | 1: Mild pain<br>2: Moderate pain; limiting instrumental ADL<br>3: Severe pain; limiting self-care ADL<br>4: Not applicable<br>5: Not applicable | - Questionnaire and medical record validation |
| Retinal detachment | Definition:<br>A disorder characterized by the separation of the inner retina layers from the underlying pigment epithelium.<br><br>Grading source:<br>St Jude modification of CTCAEv4.03<br>Eye disorders:<br>Retinal detachment | 1: Asymptomatic<br>2: Rhegmatogenous or exudative and visual acuity 20/40 or better<br>3: Rhegmatogenous or exudative detachment; operative intervention indicated; decline in vision (worse than 20/40 but better than 20/200)<br>4: Blindness (20/200 or worse) in the affected eye<br>5: Not applicable | - Questionnaire and medical record validation |
| Retinopathy | Definition:<br>A disorder involving the retina.<br><br>Grading source:<br>CTCAEv4.03<br>Eye disorders:<br>Retinopathy | 1: Asymptomatic; clinical or diagnostic observations only<br>2: Symptomatic with moderate decrease in visual acuity (20/40 or better); limiting instrumental ADL<br>3: Symptomatic with marked decrease in visual acuity (worse than 20/40); disabling; limiting self-care ADL<br>4: Blindness (20/200 or worse) in the affected eye<br>5: Not applicable | - Questionnaire and medical record validation |
| Strabismus | Definition:<br>Includes: esotropia, exotropia, hypertropia, Parinaud's syndrome, Internuclear ophthalmoplegia<br><br>Grading source:<br>St Jude modification of CTCAEv4.03<br>Eye disorders:<br>Other, specify | 1: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated<br>2: Moderate; minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental ADL<br>3: Severe or medically significant but not immediately sight threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self-care ADL<br>4: Sight-threatening consequences; urgent intervention indicated; blindness (20/200 or worse) in the affected eye<br>5: Not applicable | - Questionnaire and medical record validation |
| Visual acuity, reduced (OD) | Definition:<br>A disorder characterized by involvement of the optic nerve (second cranial nerve).<br><br>Grading source:<br>St Jude modification of CTCAEv4.03<br>Eye disorders:<br>Optic nerve disorder | 1: Asymptomatic; clinical or diagnostic observations only (reduced visual acuity corrected to 20/40 or better)<br>2: Limiting vision of the affected eye (reduced visual acuity corrected to less than 20/40 but better than 20/60)<br>3: Limiting vision in the affected eye (reduced visual acuity corrected to 20/60 but better than 20/200)<br>4: Blindness (corrected to 20/200 or worse, includes count fingers, hand motion, light perception only) in the affected eye (cortical blindness, enucleation)<br>5: Not applicable | - Questionnaire and medical record validation |

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| Visual acuity, reduced (OS) | Definition:<br>A disorder characterized by involvement of the optic nerve (second cranial nerve).<br><br>Grading source:<br>St Jude modification of CTCAEv4.03<br>Eye disorders:<br>Optic nerve disorder | 1: Asymptomatic; clinical or diagnostic observations only (reduced visual acuity corrected to 20/40 or better)<br>2: Limiting vision of the affected eye (reduced visual acuity corrected to less than 20/40 but better than 20/60)<br>3: Limiting vision in the affected eye (reduced visual acuity corrected to 20/60 but better than 20/200)<br>4: Blindness (corrected to 20/200 or worse, includes count fingers, hand motion, light perception only) in the affected eye (cortical blindness, enucleation)<br>5: Not applicable | - Questionnaire and medical record validation |
| Visual field deficit | Definition:<br>*Partly or total loss of usual visual field.*<br><br>Grading source:<br>St Jude modification of CTCAEv4.03<br>Eye disorders:<br>Optic nerve disorder | 1: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated<br>2: Moderate; minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental ADL (can't drive)<br>3: Severe or medically significant but not immediately sight threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self-care ADL (can't ambulate/navigate)<br>4: Not applicable<br>5: Not applicable | - Questionnaire and medical record validation |
| **PULMONARY** | | | |
| **Health condition** | **Definition and Grading source** | **Grading** | **ALL-STAR data** |
| Asthma | Definition:<br>A disorder characterized by a sudden contraction of the smooth muscles of the bronchial wall. Based on physician diagnosis by appropriate clinical signs and symptoms, reversible airway obstruction.<br><br>Grading source:<br>St Jude modification of CTCAEv4.03<br>Respiratory, thoracic and mediastinal disorders:<br>Bronchospasm | 1: Mild symptoms; intervention not Indicated<br>2: Symptomatic; medical intervention indicated; limiting instrumental ADL; intermittent asthma requiring short-acting beta agonists as needed<br>3: Limiting self-care ADL; oxygen saturation decreased; persistent asthma requiring daily controller medication (oral or inhaled)<br>4: Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated<br>5: Death | - Questionnaire and medical record validation<br>- Lung function tests |

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| Chronic obstructive pulmonary disease (COPD) | Definition:<br>Based on physician diagnosis by appropriate clinical signs and symptoms, irreversible airway obstruction; includes emphysema, chronic bronchitis, and mixed chronic obstructive asthma/COPD syndrome.<br><br>Grading source:<br>St Jude modification of CTCAEv4.03<br>Respiratory, thoracic and mediastinal disorders:<br>Other, specify | 1: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated<br>2: Moderate; minimal, local or noninvasive intervention indicated or initiated (inhaled medications); limiting age-appropriate instrumental ADL<br>3: Severe or medically significant but not immediately life-threatening (e.g., requiring supplementation of oxygen, systemic corticosteroids, BIPAP, or CPAP); hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self-care ADL<br>4: Life-threatening consequences; urgent intervention indicated<br>5: Death | - Questionnaire and medical record validation<br>- Lung function tests |
| Epistaxis, chronic/recurrent | Definition:<br>Defined as 3 events in last 6 months<br><br>Grading Source:<br>CTCAEv4.03<br>Respiratory, thoracic and mediastinal disorders:<br>Epistaxis | 1: Mild symptoms; intervention not Indicated<br>2: Moderate symptoms; medical intervention indicated (e.g., nasal packing, cauterization; topical vasoconstrictors)<br>3: Transfusion, radiologic, endoscopic, or operative intervention indicated (e.g., hemostasis of bleeding site)<br>4: Life-threatening consequences; urgent intervention indicated<br>5: Death | - Questionnaire and medical record validation |
| Obstructive sleep apnea | Definition:<br>A condition with narrowing or collapse of the throat causing repeatedly obstructive sleep apnoea events.[36]<br><br>Grading source:<br>St Jude category and grading according to multidisciplinary team consensus | 1: Documentation of apnea; no need for medication<br>2: Documentation of mild apnea; behavioral intervention initiated or indicated<br>3: Documentation of moderate apnea; CPAP initiated or indicated<br>4: Documentation of severe apnea with secondary complications (CHF, HTN, headache)<br>5: Not applicable | - Questionnaire and medical record validation |

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| Obstructive ventilatory defect | Definition:<br>Defined by FEV1 < 80% predicted and <LLN. Disorders associated with this pattern and reduced FEV1/FVC ratio (obstructive ventilatory defect) include: asthma, COPD, tracheobronchomalacia, obliterative bronchiolitis and bronchiectasis. Disorders associated with this pattern and normal or increased FEV1/FVC (possible restrictive ventilatory defect, confirm with TLC) include pulmonary fibrosis, other interstitial lung diseases, chest wall disorders)<br><br>Grading source;<br>New category and Grading source introduced by St Jude:<br><br>Pellegrino et al, Interpretative strategies for lung function tests. Eur Resp J 2005;26:948-968. Table 6 | 1: FEV1 (percentages of observed FEV1 related to its predicted value): 79-70% predicted<br>2: FEV1: 69-50% predicted<br>3: FEV1: 49-35% predicted<br>4: FEV1: <35% predicted<br>5: Not applicable | - Questionnaire and medical record validation<br>- Lung function tests |
| Pleural space disorders | Definition:<br>Includes: pleural effusions, chylothorax, hemothorax<br><br>Grading source:<br>St Jude modification of CTCAEv4.03<br>Respiratory, thoracic and mediastinal disorders<br>Pneumothorax | 1: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated<br>2: Moderate to severe symptoms and non-operative intervention indicated (e.g., tube placement without sclerosis)<br>3: Sclerosis and/or operative intervention indicated; hospitalization indicated<br>4: Life-threatening consequences; urgent intervention indicated<br>5: Death | - Questionnaire and medical record validation |
| Pneumonitis | Definition:<br>A disorder characterized by inflammation focally or diffusely affecting the lung parenchyma.<br><br>Grading source:<br>St Jude modification of CTCAEv4.03<br>Respiratory, thoracic and mediastinal disorders:<br>Pneumonitis | 1: Not applicable<br>2: Symptomatic; medical intervention indicated; limiting instrumental ADL<br>3: Severe symptoms; limiting self-care ADL; oxygen indicated<br>4: Life-threatening respiratory compromise; urgent intervention indicated (e.g., tracheotomy or intubation)<br>5: Death | - Questionnaire and medical record validation |

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| Pulmonary diffusion defect | Definition:<br>DLCOcorr < 75%<br>predicted and <LLN. Includes: pneumonitis, pulmonary fibrosis, other interstitial lung diseases, pulmonary vascular disorders and emphysema)<br><br>Grading source:<br>New category and Grading source introduced by St Jude:<br><br>Pellegrino et al, Interpretative strategies for lung function tests. Eur Resp J 2005;26:948-968. Table 14 | 1: DLCO: 74-60% predicted<br>2: DLCO: <60%-40% predicted<br>3: DLCO: <40% predicted<br>4: Not applicable<br>5: Not applicable | - Questionnaire and medical record validation<br>- Lung function tests |
| Pulmonary embolism | Definition:<br>A disorder characterized by occlusion of a vessel by a thrombus that has migrated from a distal site via the blood stream.<br><br>Grading source:<br>St Jude modification of CTCAEv4.03<br>Vascular disorders:<br>Thromboembolic event | 1: Not applicable<br>2: Not applicable<br>3: Urgent medical intervention indicated<br>4: Life-threatening with hemodynamic or neurologic instability<br>5: Death | - Questionnaire and medical record validation |
| Respiratory tract hemorrhage | Definition:<br>A disorder characterized by bleeding from the bronchial wall and/or lung parenchyma.<br><br>Grading source:<br>St Jude modification of CTCAEv4.03<br>Respiratory, thoracic and mediastinal disorders:<br>Bronchopulmonary hemorrhage | 1: Mild symptoms; intervention not Indicated<br>2: Moderate symptoms; medical intervention indicated<br>3: Transfusion, radiologic, endoscopic, or operative intervention indicated (e.g., hemostasis of bleeding site)<br>4: Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated<br>5: Death | - Questionnaire and medical record validation |

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| Restrictive ventilatory defect | Definition:<br>Defined by TLC < 75% predicted and <LLN. Includes: pulmonary fibrosis and other interstitial lung disease, pneumonitis, chest wall disorders.<br><br>Grading source:<br>New category and Grading source introduced by St Jude:<br><br>American Thoracic Society, Lung Function Testing: Selection of Reference Values and Interpretative Strategies. Am Rev Respir Dis 1991;144:1202-1218. Table 13 | 1: TLC: 74 -70%<br>2: TLC: 69 - 60% predicted; limiting instrumental ADL<br>3: TLC: <60% predicted; limiting self-care ADL<br>4: Not applicable<br>5: Not applicable | - Questionnaire and medical record validation<br>- Lung function tests |
| Tracheal aspiration | Definition:<br>A disorder characterized by inhalation of solids or liquids into the lungs.<br><br>Grading source:<br>ST Jude modification of CTCAEv4.03 Respiratory, thoracic and mediastinal disorders:<br>Aspiration | 1: Asymptomatic; clinical or diagnostic observations only; intervention not indicated<br>2: Altered eating habits; coughing or choking episodes after eating or swallowing; medical intervention indicated (e.g., suction or oxygen)<br>3: Dyspnea and pneumonia symptoms (e.g., aspiration pneumonia); hospitalization indicated; unable to aliment orally<br>4: Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated<br>5: Death | - Questionnaire and medical record validation |
| Tracheal stenosis | Definition:<br>A disorder characterized by a narrowing of the trachea.<br><br>Grading source:<br>CTCAEv4.03 Respiratory, thoracic and mediastinal disorders:<br>Tracheal stenosis | 1: Asymptomatic; clinical or diagnostic observations only; intervention not indicated<br>2: Symptomatic (e.g., noisy airway breathing), but causing no respiratory distress; medical management indicated (e.g., steroids)<br>3: Stridor or respiratory distress limiting self-care ADL; endoscopic intervention indicated (e.g., stent, laser)<br>4: Life-threatening airway compromise; urgent intervention indicated (e.g., tracheotomy or intubation)<br>5: Death | - Questionnaire and medical record validation |

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| PSYCHIATRIC | | | |
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| **Health condition** | **Definition and Grading source** | **Grading** | **ALL-STAR data** |
| Anxiety | Definition:<br>Validated patient reported outcome measure**.** Threshold of clinical intervention and impact on ADL<br><br>Grading source:<br>St Jude<br>*"Detailed grading criteria for neuropsychological outcomes were outlined by psychologists incorporating patient-reported outcomes and the results of validated cognitive and psychological measures and comprehensive psychosocial evaluations by study social workers".*[1]<br><br>ALL-STAR modification: Diagnosed by psychiatrist. | 1: Score >1 SD above the mean and mental health intervention not indicated.<br>2: Score >1.5 SD above the mean; Score ≤1.5 SD above the mean and treatment limited to 1 initiated or indicated mental health intervention; symptoms interfere with social or occupational functioning<br>3: Score >2 SD above the mean; Score ≤2 SD and >1.5 SD above the mean and >1 mental health intervention initiated or indicated; symptoms interfere with self-care<br>4: Hospitalization due to symptoms of anxiety indicated<br>5: Death | - Questionnaire and medical record validation |
| Depression | Definition:<br>Validated patient reported outcome measure<br>Threshold of clinical intervention and impact on ADL<br><br>Grading source:<br>St Jude<br>*"Detailed grading criteria for neuropsychological outcomes were outlined by psychologists incorporating patient-reported outcomes and the results of validated cognitive and psychological measures and comprehensive psychosocial evaluations by study social workers".*[1]<br><br>ALL-STAR modification: Diagnosed by psychiatrist. | 1: Score >1 SD above the mean and mental health intervention not indicated<br>2: Score >1.5 SD above the mean; Score ≤1.5 SD above the mean and treatment limited to 1 initiated or indicated mental health intervention; symptoms interfere with social or occupational functioning<br>3: Score >1.5 above the mean and patient reports suicide ideation; Score >2 SD above the mean; Score ≤2 SD and >1.5 SD above the mean and >1 mental health intervention initiated or indicated; symptoms interfere with self-care<br>4: Hospitalization due to symptoms of depression indicated<br>5: Death | - Questionnaire and medical record validation |

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| Other psychiatric disorders | Definition<br>A disorder characterized by personality change, impaired functioning, and loss of touch with reality. It may be a manifestation of schizophrenia, bipolar disorder or brain tumor.<br>E.g., delirium; delusions; hallucinations; paranoia; psychosis<br><br>Grading source:<br>St Jude modification of CTCAEv4.03<br>Psychiatric: Psychosis<br><br>ALL-STAR modification: Diagnosed by psychiatrist. | 1: Mild symptoms reported, and mental health intervention not indicated<br>2: Moderate symptoms reported; treatment limited to 1 initiated or indicated mental health intervention; symptoms interfere with social or occupational functioning<br>3: Severe symptoms reported; >1 mental health intervention initiated or indicated; symptoms interfere with self-care<br>4: Hospitalization or urgent intervention due to symptoms is indicated<br>5: Death | - Questionnaire and medical record validation |
| **RENAL / URINARY** | | | |
| **Health condition** | **Definition and Grading source** | **Grading** | **ALL-STAR data** |
| Acute kidney injury | Definition:<br>A disorder characterized by the acute loss of renal function and is traditionally classified as pre-renal (low blood flow into kidney), renal (kidney damage) and postrenal causes (ureteral or bladder outflow obstruction).<br><br>Grading source:<br>St Jude modification of CTCAEv4.03<br>Renal and urinary disorders:<br>Acute kidney injury | 1: Creatinine 1.5-2.0 x above age-specific ULN<br>2: Creatinine 2 - 3 x above age-specific ULN<br>3: Creatinine >3 x age-specific ULN or >4.0 mg/dL; hospitalization indicated<br>4: Life-threatening consequences; dialysis indicated<br>5: Death | - Questionnaire and medical record validation<br>- Creatinine<br>- Cystatin-C<br>- eGFR |
| Chronic hematuria | Definition: A disorder characterized by laboratory test results that indicate blood in the urine. Defined as > 5 RBCs/hpf documented on more than one urinalysis.<br><br>Grading source:<br>St Jude modification of CTCAEv4.03<br>Renal and urinary disorders:<br>Hematuria | 1: Asymptomatic; clinical or diagnostic observations only; intervention not indicated<br>2: Symptomatic; urinary catheter or bladder irrigation indicated; limiting instrumental ADL<br>3: Gross hematuria; transfusion, IV medications or hospitalization indicated; elective invasive intervention indicated; limiting self-care ADL<br>4: Life-threatening consequences; urgent invasive intervention indicated<br>5: Death | - Questionnaire and medical record validation |

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| Chronic kidney disease | Definition:<br>A disorder characterized by gradual and usually permanent loss of kidney function resulting in renal failure. Includes CKD requiring dialysis/transplant<br><br>Grading source:<br>St Jude modification of CTCAEv4.03<br>Renal and urinary disorders:<br>Chronic kidney disease<br><br>eGFR estimated used in the KDIGO estimating equations:<br>http://www.kdigo.org/clinical_practice_guidelines/pdf/CKD/KDIGO_2012_CKD_GL.pdf<br><br>ALL-STAR modification: eGFR estimated according to CKiDkrea-cysC-equation in children[37] and CKD-EPI$_{crea}$-equation in adults[38]. | 1: eGFR (estimated Glomerular Filtration Rate) or CrCl (creatinine clearance) <LLN – 60 ml/min/1.73 m$^2$ AND proteinuria 1+ present; urine protein/creatinine >0.5<br>2: eGFR or CrCl 59-30 ml/min/1.73 m$^2$; medication (e.g., electrolytes, ACE inhibition, etc….) indicated or initiated<br>3: eGFR or CrCl 29-15 ml/min/1.73 m$^2$<br>4: eGFR or CrCl <15 ml/min/1.73 m$^2$; dialysis or renal transplant indicated or initiated/performed<br>5: Death | - Questionnaire and medical record validation<br>- eGFR |
| Incontinence | Definition:<br>A disorder characterized by inability to control the flow of urine from the bladder.<br><br>Grading source:<br>CTCAEv4.03<br>Renal and urinary disorders:<br>Urinary incontinence | 1: Occasional (e.g., with coughing, sneezing, etc.), pads not indicated<br>2: Spontaneous; pads indicated; limiting instrumental ADL<br>3: Intervention indicated (e.g., clamp, collagen injections); operative intervention indicated; limiting self-care ADL<br>4: Not applicable<br>5: Not applicable | - Questionnaire and medical record validation |
| Obstructive uropathy | Definition:<br>A disorder characterized by blockage of the normal flow of contents of the urinary tract. Includes: urinary tract stenosis; urinary tract stricture.<br><br>Grading source:<br>St Jude modification of CTCAEv4.03<br>Renal and urinary disorders:<br>Urinary tract obstruction | 1: Asymptomatic; clinical or diagnostic observations only<br>2: Symptomatic but no hydronephrosis, sepsis or renal dysfunction; urethral dilation, urinary or suprapubic catheter indicated<br>3: Symptomatic and altered organ function (e.g., hydronephrosis, or renal dysfunction); elective invasive intervention indicated<br>4: Life-threatening consequences; urgent invasive intervention indicated<br>5: Death | - Questionnaire and medical record validation |

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| Urinary bladder dysfunction | Definition:<br>A disorder characterized by a sudden compelling urge to urinate. Includes: dysfunctional voiding, hypertonic bladder, urinary frequency, urinary hesitancy.<br><br>Grading source<br>St Jude modification of CTCAEv4.03<br>Renal and urinary disorders:<br>Urinary frequency<br>Urinary urgency | 1: Present<br>2: Limiting instrumental ADL; medical management indicated or initiated<br>3: Surgical management indicated or initiated (e.g., trans-electrical nerve stimulation, sacral neural modulation)<br>4: Not applicable<br>5: Not applicable | - Questionnaire and medical record validation |
| Urinary tract calculi | Definition:<br>A disorder characterized by the formation of crystals in the pelvis of the kidney. Includes: renal calculi, bladder stone/calculi, ureteral calculi.<br><br>Grading source:<br>St Jude modification of CTCAEv4.03<br>Renal and urinary disorders:<br>Renal calculi | 1: Asymptomatic or mild symptoms; occasional use of nonprescription analgesics indicated<br>2: Symptomatic; oral antiemetics indicated; around the clock nonprescription analgesics or any oral narcotic analgesics indicated<br>3: Hospitalization indicated; IV intervention (e.g., analgesics, antiemetics); elective invasive intervention indicated<br>4: Life-threatening consequences; urgent invasive intervention indicated<br>5: Death | - Questionnaire and medical record validation |
| Vesicoureteral reflux, acquired | Definition:<br>Abnormal retrograde flow of urine from the bladder to the ureter and potentially the kidney.[39]<br><br>Grading source:<br>St Jude modification of CTCAEv4.03<br>Renal and urinary disorders:<br>Other, specify | 1: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated<br>2: Moderate, local or noninvasive intervention indicated; limiting instrumental ADL<br>3: Severe or medically significant but not immediately life threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self-care ADL<br>4: Life-threatening consequences; urgent intervention indicated<br>5: Death | - Questionnaire and medical record validation |
| **REPRODUCTIVE / GENITAL** | | | |
| **Health condition** | **Definition and Grading source** | **Grading** | **ALL-STAR data** |
| Abnormal sperm concentration<br><br>(Includes: oligospermia, azoospermia) | Definition:<br>A disorder characterized by a decrease or complete absence of spermatozoa in the semen.<br><br>St Jude modification of<br>Reproductive system and breast disorders:<br>Oligospermia<br>Azoospermia | 1: Not applicable<br>2: Sperm concentration > 0 but < 15 million spermatozoa/mL<br>3: Absence of sperm in ejaculate<br>4: Not applicable<br>5: Not applicable | - Questionnaire and medical record validation |

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| Cervical dysplasia | Definition:<br>Abnormal growth of cells on the surface of the cervix.[40]<br><br>Grading source:<br>St Jude modification of<br>CTCAE v4.03<br>Reproductive system and breast disorder:<br>Other, specify | 1: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated<br>2: Moderate; minimal, local or non-invasive intervention indicated; limiting age appropriate instrumental ADL (e.g., colposcopy)<br>3: Severe or medically significant but not immediately life threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self-care ADL (e.g., conization for carcinoma-in-situ)<br>4: Not applicable<br>5: Not applicable | - Questionnaire and medical record validation |
| Dysfunctional uterine bleeding | Definition:<br>A disorder characterized by abnormally heavy vaginal bleeding during menses.<br><br>Grading source:<br>CTCAE v4.03<br>Reproductive system and breast disorders<br>Menorrhagia | 1: Mild; iron supplements indicated<br>2: Moderate symptoms; medical intervention indicated (e.g., hormones)<br>3: Severe; transfusion indicated; surgical intervention indicated (e.g., hysterectomy)<br>4: Life-threatening consequences; urgent intervention indicated<br>5: Death | - Questionnaire and medical record validation |
| Endometriosis | Definition:<br>The presence of endometrial tissue outside the uterine cavity.[41]<br><br>Grading source:<br>St Jude modification of<br>CTCAE v4.03<br>Reproductive system and breast disorders:<br>Other, specify | 1: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated<br>2: Moderate; minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental ADL (e.g., medical management)<br>3: Severe or medically significant but not immediately life threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self-care ADL (e.g., surgical intervention)<br>4: Life-threatening consequences; urgent intervention indicated<br>5: Death | - Questionnaire and medical record validation |
| Erectile dysfunction | Definition:<br>A disorder characterized by the persistent or recurrent inability to achieve or to maintain an erection during sexual activity.<br><br>Grading source:<br>CTCAE v4.03<br>Reproductive system and breast disorders:<br>Erectile dysfunction | 1: Decrease in erectile function (frequency or rigidity of erections) but intervention not indicated (e.g., medication or use of mechanical device, penile pump)<br>2: Decrease in erectile function (frequency/ rigidity of erections), erectile intervention indicated, (e.g., medication or mechanical devices such as penile pump)<br>3: Decrease in erectile function (frequency/ rigidity of erections) but erectile intervention not helpful (e.g., medication or mechanical devices such as penile pump); placement of a permanent penile prosthesis indicated (not previously present)<br>4: Not applicable<br>5: Not applicable | - Questionnaire and medical record validation |
| Genitourinary adhesions | Definition:<br>*Intraabdominal formation of fibrous bands between genital and urinary organs*.<br><br>Grading source:<br>St Jude modification of CTCAE v4.03<br>Reproductive system and breast disorders:<br>Other, specify | 1: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated<br>2: Moderate; minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental ADL<br>3: Severe or medically significant but not immediately life threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self-care ADL<br>4: Life-threatening consequences; urgent intervention indicated<br>5: Death | - Questionnaire and medical record validation |

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| Hypogonadism, central (hypogonadotropic) | Definition:<br>A finding based on laboratory test results that indicate abnormal levels of gonadotrophin hormone in a blood specimen.<br><br>Grading source:<br>St Jude modification of<br>CTCAE v4.03<br>Investigations:<br>Blood gonadotropin abnormal | 1: Asymptomatic; clinical or diagnostic observations only; intervention not indicated<br>2: Symptomatic; medical intervention indicated or initiated; limiting instrumental ADL<br>3. Severe symptoms; medical intervention indicated or initiated; limiting self-care ADL<br>4. Not applicable<br>5. Not applicable | - Questionnaire and medical record validation<br>- FSH<br>- LH<br>- Testosterone<br>- SHBG |
| Leydig cell insufficiency | Definition:<br>Leydig cell failure resulting from damage or loss of the machinery required for testosterone synthesis and release.[42]<br><br>Grading source:<br>St Jude modification of<br>CTCAE v4.03<br>Reproductive system and breast disorders:<br>Other, specify | 1: Asymptomatic; clinical or diagnostic observations only; intervention not indicated<br>2: Symptomatic; medical intervention indicated or initiated; limiting instrumental ADL<br>3: Severe symptoms; medical intervention indicated or initiated; limiting self-care ADL<br>4: Not applicable<br>5: Not applicable | - Questionnaire and medical record validation<br>- FSH<br>- LH<br>- Testosterone<br>- SHBG |
| Polycystic ovarian syndrome | Definition:<br>A clinical syndrome characterized by clinical or biochemical hyperandrogenism, oligo-anovulation, and polycystic ovarian morphology.[43]<br><br>Grading source:<br>St Jude modification of<br>CTCAE v4.03<br>Reproductive system and breast disorders<br>Other, specify | 1: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated (e.g., mild signs/symptoms of hyperandrogenemia)<br>2: Moderate; minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental ADL (e.g., more severe hirsutism, irregular menses; need for metformin or hormone replacement)<br>3: Severe or medically significant but not immediately life threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self-care ADL (e.g., need for surgery for cyst or bleed)<br>4: Not applicable<br>5: Not applicable | - Questionnaire and medical record validation |
| Precocious puberty | Definition:<br>A disorder characterized by unusually early development of secondary sexual features; the onset of sexual maturation begins usually before age 8 for girls and before age 9 for boys.<br><br>Grading source:<br>St Jude modification of<br>CTCAE v4.03<br>Endocrine disorders:<br>Precocious puberty | 1: Not applicable<br>2: Physical signs and biochemical markers of puberty for females <8 years and males <9 years<br>3: Not applicable<br>4: Not applicable<br>5: Not applicable | - Questionnaire and medical record validation<br>- Tanner stage<br>- Testicular volumes |

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| | | | |
|---|---|---|---|
| Primary ovarian failure | Definition:<br>A disorder characterized by ovarian failure before the age of 40. Symptoms include hot flashes, night sweats, mood swings and a decrease in sex drive.<br><br>Grading source:<br>CTCAE v4.03<br>Reproductive system and breast disorders: Premature menopause | 1: Not applicable<br>2: Not applicable<br>3: Present<br>4: Not applicable<br>5: Not applicable | - Questionnaire and medical record validation<br>- FSH<br>- Estradiol |
| Prostatic hypertrophy, benign | Definition:<br>A disorder characterized by compression of the urethra secondary to enlargement of the prostate gland. This results in voiding difficulties (straining to void, slow urine stream, and incomplete emptying of the bladder).<br><br>Grading source:<br>CTCAEv4.03<br>Reproductive system and breast disorders: Prostatic obstruction | 1: Diagnostic observations only; intervention not indicated<br>2: Mild symptoms; elective intervention indicated<br>3: Severe symptoms; elective operative intervention indicated<br>4: Not applicable<br>5: Not applicable | - Questionnaire and medical record validation |
| Vaginal fistula | Definition:<br>A disorder characterized by an abnormal communication between a female reproductive system organ and another organ or anatomic site.<br><br>Grading source:<br>St Jude modification of CTCAE v4.03<br>Reproductive system and breast disorders: Female genital tract fistula | 1: Asymptomatic clinical or diagnostic observations only; intervention not indicated<br>2: Symptomatic and intervention not indicated<br>3: Severe symptoms; elective operative intervention indicated<br>4: Life-threatening consequences; urgent intervention indicated<br>5: Death | - Questionnaire and medical record validation |
| Vaginal stenosis | Definition:<br>A disorder characterized by a narrowing of the vaginal canal.<br><br>Grading source:<br>St Jude modification of CTCAE v4.03<br>Reproductive system and breast disorders: Vaginal stricture | 1: Asymptomatic; mild vaginal shortening or narrowing<br>2: Vaginal narrowing and/or shortening not interfering with physical examination<br>3: Vaginal narrowing and/or shortening interfering with the use of tampons, sexual activity or physical examination (e.g., surgical intervention indicated or performed)<br>4: Not applicable<br>5: Not applicable | - Questionnaire and medical record validation |

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| NEOPLASMS | | | |
|---|---|---|---|
| **Health condition** | **Definition and Grading source** | **Grading** | - **ALL-STAR data** |
| Benign neoplasms | Definition:<br>Neoplasms benign, malignant and unspecified (incl cysts and polyps).<br>Other, specify<br><br>Grading Source<br>ST Jude Modification of CTCAE v4.03<br>Neoplasms, benign, malignant | 1: Low grade or benign neoplasms where surgical intervention is not indicated; observation or minimally invasive biopsy only (e.g. meningioma followed by MRI only or gastrointestinal polyps diagnosed and resected during colonoscopy)<br><br>2: Any low-grade or benign neoplasm requiring surgical intervention more than a minimally invasive biopsy. Excludes CNS or cardiothoracic surgical interventions (e.g. fibroadenomas, thyroid adenomas, gastrointestinal polyps requiring surgical resection)<br><br>3: Any low-grade or benign neoplasm requiring CNS or cardiothoracic surgical intervention (e.g. meningioma or myxoma requiring intervention)<br><br>4: Life-threatening consequences; urgent intervention indicated<br><br>5: Death | - Questionnaire and medical record validation |
| Malignant neoplasms | Definition:<br>Neoplasms benign, malignant and unspecified (incl cysts and polyps).<br>Other, specify<br><br>Grading Source<br>ST Jude Modification of CTCAE v4.03<br>Neoplasms, benign, malignant | 1: Asymptomatic or mild symptoms; clinical or diagnostic observations only; low-grade neoplasms where intervention is not indicated (e.g. cervical dysplasia/CIN and teratoma incidentally identified on imaging)<br><br>2: Moderate symptoms; minimal, local, or noninvasive intervention indicated; limiting age appropriate instrumental ADL; low-grade, non-metastatic neoplasms (e.g. cervical carcinoma *in situ*, cervical lymph node paraganglioma, basal cell carcinoma, squamous cell carcinoma, parotid carcinoma)<br><br>3: Severe or medically significant, but not immediately life-threatening; hospitalization indicated; disabling; limiting self-care ADL; high-grade neoplasms where single-treatment therapy required (surgery, radiation with or without chemotherapeutic agent; e.g. breast cancer if *in situ*, prostate cancer, meningioma requiring intervention, bladder carcinoma, thyroid cancer, carcinoid, squamous cell carcinoma cervix, glioma, astrocytoma, gastrointestinal stromal tumor)<br><br>4: Life-threatening consequences; urgent intervention indicated; high-grade neoplasms where multimodal therapy required or more than one chemotherapy agent used (e.g. MDS, AML, ALL, Hodgkin lymphoma, non-Hodgkin lymphoma, non-*in situ*/invasive breast cancer, osteosarcoma, Ewing sarcoma, primitive neuroectodermal tumor, soft tissue sarcoma, renal cancer, anaplastic CNS Timor, glioblastoma, carcinoma of head/neck, liver cancer, lung cancer, mesothelioma, melanoma)<br><br>5: Death | - |

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Supplementary Table 2.
Overview of the ALL-STAR questionnaire content and versions.

| **Domains** | **Items** | **Age < 15, M+F Proxy** | **Age 15-18 M+F Proxy** | **Age 15-18 M Self** | **Age 15-18 F Self** | **Age >= 18 M Self** | **Alder >=18 F Self** |
|---|---|---|---|---|---|---|---|
| Contact info | **Contact info** | x | x | x | X | x | x |
| | **Relation to subject** | x | x | | | | |
| Health care | **Leukemia follow-up** | x | x | x | x | x | X |
| | **Use of health care[1]** | x | x | x | x | x | X |
| Medicine | **Use of medicine[2]** | x | x | x | x | x | X |
| Health conditions | **Diagnoses and symptoms[3]** | x | x | x | x | x | X |
| | **Puberty[3]** | x | x | x | x | x | X |
| | **Fertility[3]** | (x) | (x) | x | x | x | X |
| | **Erectile dysfunction[3]** | | | | | X | |
| | **Surgeries** | x | x | x | x | x | X |
| | **Cancer (other than leukemia)** | x | x | x | x | x | X |
| Familiar dispositions | **Familiar dispositions** | x | x | | | x | X |
| | **Parent height and weight** | x | x | | | x | x |
| Health behavior | **Smoking** | x | x | x | x | x | X |
| | **Alcohol** | x | x | x | x | x | X |
| | **Drugs** | | | x | x | x | x |
| | **Level of physical activity** | x | x | x | x | x | X |
| | **Sedentary behavior** | x | x | x | x | x | X |
| | **Extracurricular activities** | x | x | x | x | x | X |
| | **Diet** | x | x | x | x | x | X |
| Socioeconomics | **Family structure** | x | x | x | x | x | X |
| | **Relationships/marriage/divorce** | | | x | x | x | x |
| | **Type of housing** | x | x | x | x | x | X |
| | **Educational achievements and difficulties** | x | x | x | x | x | X |
| | **Parents educational level** | x | x | x | x | x | x |
| | **Employment status** | | | x | x | x | X |
| | **Household income** | x | x | | | x | X |
| Psychosocial instruments[4] | **Health-related quality of life** | | | | | | |
| | **Fatigue** | x | x | x | x | x | X |
| | **Social relations** | x | x | x | x | x | x |
| | **Anxiety** | x | x | x | x | x | X |
| | **Depressive symptoms** | x | x | x | x | x | X |
| | **Post-traumatic stress** | x | x | x | x | x | X |
| | **Post-traumatic growth** | | | x | x | x | X |
| Cognitive[4] | **Executive function** | x | x | x | x | x | x |

1) Including active leukemia follow-up for survivors
2) Prescription- and non-prescription medicine / supplements during the preceding 12 months
3) Respondents are instructed to only answer yes to specific diagnoses if confirmed by a medical doctor. Symptoms are reported subjectively. Respondents are instructed to answer yes if the symptom/condition is present or has been present at any time point. If respondents answer yes, pop-up items require about 1) age at first occurrence, 2) multiple events where applicable, 3) if the condition/symptom is present today, and 4) how much the condition/symptom impacts on every-day life (on a 5-point Likert like scale). Survivors (not controls) are also asked whether the condition was present prior to leukemia diagnosis.
5) An overview of the standardized instruments used to evaluate emotional and cognitive function is provided in S5

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Supplementary Table 3. ALL-STAR examination program and clinical investigators.

| **Examination program** | | |
|---|---|---|
| **Time** | **Clinic** | **Activity/Investigations** |
| 7.30–8.00 am | ALL-STAR clinic | - Confirmation of consent<br>- Receipt of morning urine sample (collected at home)<br>- Measurement of height, weight and waist circumference<br>- Drawing of blood samples<br>(collection of samples for central lab) |
| 8-00–8.30 am | | *Breakfast* |
| 8.30-10.00 am | ALL-STAR clinic | - Tanner evaluation<br>- Questionnaires<br>  o Validation of ALL-STAR questionnaire completed prior to the examination day<br>  o Total Neuropathy Score (TNS) self-report items<br>  o COMPASS31 items<br>- TNS clinical tests<br>- Electrophysiological evaluation<br>- Holter record<br>- Spot urine dip stick test |
| 10.00–11.15 am | Physical test lab | - Physical performance tests<br>- Cardiorespiratory fitness bike test<br>- Dispensing of accelerometer and instructions for 7-day recording |
| 11.30–12.00 am | Department of radiology, ultrasound section | - Ultrasound scan of<br>  o Liver and gallbladder<br>  o Spleen<br>  o Pancreas<br>  o kidney |
| 12.15–12.45 pm | Department of cardiology, imaging section | - Speckle Tracking Echocardiography<br>- 12-Electrocardiogram |
| 12.45–13.30 pm | | *Lunch* |
| 13.30–13.50 | Department of Growth and reproduction | - DXA scan<br>  o Lumbar spine scan<br>  o Dual-femur bone scan<br>  o Whole body scan |
| 14.00–1530 | Department of cardiology, imaging section | - Cardiac MRI scan |
| 15.30–16 | | *Break and snacks* |
| 16.00–17 | Department of paediatrics, Division of Pulmonology | - Spirometry<br>- Nitrogen multiple breath washout<br>- Single breath diffusion capacity |
| 17.00–17.45 | ALL-STAR clinic | - Orofacial and dental evaluation<br>- Measurement of whole saliva flow rates<br>- Collection of whole saliva samples |

Abbreviations: COMPASS31 = Composite Autonomic Symptom Score with 31 items; TNS = Total Neuropathy Score; MRI = magnetic resonance imaging

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**Clinical investigators.**

Measurement of height, weight, waist circumference, pubertal evaluation, electrocardiogram (ECG), Holter recording, physical tests, cardiopulmonary exercise test (CPET), pulmonary function tests, dual-energy X-ray absorptiometry (DXA) and neurological tests are performed by a trained and certified research team consisting of nurses and physicians at each site. Dental evaluations are performed by one dentist at one site only. Abdominal ultrasound scans are performed and evaluated by the same two ultrasound radiologists. Cardiac imaging is performed by trained echo technicians and MR radiographs at each site and images are evaluated centrally by the same team of blinded cardiologists. Standard blood tests are performed at the central laboratory at each university hospital. For tests where methodology differ at the two sites, blood samples are sent for central analysis at Copenhagen University Hospital. An advisory board consisting of physicians and senior researchers within the fields of pediatric oncology, endocrinology, physiotherapy, neurology, cardiology, pulmonology, gastroenterology, nephrology, immunology, ophthalmology, odontology, and diagnostic imaging perform continuous supervision of procedures and collected data across both study sites.

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Supplementary Table 4. Standardized questionnaire instruments.

| **Psychosocial standardized instruments included in the ALL-STAR questionnaire** | | |
|---|---|---|
| Domain | Instrument and version | ALL-STAR respondent group |
| Health-related quality of life | Pediatric Quality of Life Inventory (PedsQL)® core, version 4.0, young adults, self-report | Survivors and controls, aged > 18 |
| | PedsQL® core, version 4.0, teenagers | Survivors and controls, aged 15–18 |
| | PedsQL® core, version 4.0, teenagers, proxy-report | Parents/guardians for survivors and controls aged 15–18 |
| | PedsQL® core, version 4.0, children aged 8-12, proxy report | Parents/guardians for survivors and controls aged 8-15 |
| Fatigue | PedsQL® Fatigue, version 4.0, young adults, self-report | Survivors and controls, aged > 18 |
| | PedsQL® Fatigue, version 4.0, teenagers, self-report | Survivors and controls, aged 15–18 |
| | PedsQL® Fatigue, version 4.0, teenagers, proxy-report | Parents/guardians for survivors and controls aged 15–18 |
| | PedsQL® Fatigue, version 4.0, children aged 8-12, proxy-report | Parents/guardians for survivors and controls aged 8-15 |
| Social relations | PROMIS® Emotional support – Short Form 8a, adult, self-report | Survivors and controls, aged > 18 |
| | PROMIS® Pediatric Item bank v.1.0, Family Relationships – Short Form 8a | Survivors and controls, aged 15–18 |
| | PROMIS® Pediatric Item bank v.2.0, Peer Relationships – Short Form 8a | Survivors and controls, aged 15–18 |
| | PROMIS® Parent Proxy Item bank v.1.0, Family Relationships – Short Form 8a | Parents/guardians for survivors and controls aged <18 |
| | PROMIS® Parent Proxy Item bank v.2.0, Family Relationships – Short Form 7a | Parents/guardians for survivors and controls aged <18 |
| Anxiety | PROMIS® Item bank v. 1.0, Emotional distress – Anxiety -Short Form 8a | Survivors and controls, aged > 18 |
| | PROMIS® Pediatric Item bank v. 2.0, Emotional distress – Anxiety - Short Form 8a | Survivors and controls, aged 15–18 |
| | PROMIS® Parent Proxy Item bank v. 2.0, Emotional distress – Short Form 8a | Parents/guardians for survivors and controls aged <18 |
| Depressive symptoms | PROMIS® Item bank v. 1.0, Emotional distress – Depression -Short Form 8a | Survivors and controls, aged > 18 |
| | PROMIS® Pediatric Item bank v. 2.0, Emotional distress – Depressive Symptoms - Short Form 8a | Survivors and controls, aged 15–18 |
| | PROMIS® Parent Proxy Item bank v. 2.0, Emotional distress – Depressive Symptoms - Short Form 6a | Parents/guardians for survivors and controls aged <18 |
| Post-traumatic stress | Impact of event scale – revised® (IES-R), age > 18, self-report | Survivors, aged > 18 |
| | Child Revised Impact og Events Scale® (CRIES)-8, age 8-18, self-report | Survivors, aged 15–18 |
| | CRIES-13®, age 8-18, proxy report | Parents/guardians for survivors and controls aged 8–18 |
| Post traumatic growth | Post traumatic Growth Inventory® (PTG) | Survivors, aged > 15 |
| Executive function | Behavior Rating Inventory of Executive Function® (BRIEF)-V, ages 18-90, self-report | Survivors and controls, aged > 18 |
| | BRIEF-SR®, age 11-18, self-report | Survivors and controls, aged 15–18 |
| | BRIEF®, age 5-18, proxy-report | Parents/guardians for survivors and controls aged <18 |

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**STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology***
**Checklist for cohort, case-control, and cross-sectional studies (combined)**

| Section/Topic | Item # | Recommendation | Reported on page # |
|---|---|---|---|
| **Title and abstract** | 1 | (*a*) Indicate the study's design with a commonly used term in the title or the abstract | 3 |
| | | (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found | 3 |
| **Introduction** | | | |
| Background/rationale | 2 | Explain the scientific background and rationale for the investigation being reported | 5-6 |
| Objectives | 3 | State specific objectives, including any pre-specified hypotheses | 6+8 |
| **Methods** | | | |
| Study design | 4 | Present key elements of study design early in the paper | 6 |
| Setting | 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection | 7 |
| Participants | 6 | (*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up<br>*Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls<br>*Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants | 7 |
| | | (*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed<br>*Case-control study*—For matched studies, give matching criteria and the number of controls per case | 7 |
| Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable | 7-16 + supplementary table 1 |
| Data sources/ measurement | 8* | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group | 7-16 + supplementary table 1 |
| Bias | 9 | Describe any efforts to address potential sources of bias | 19 |
| Study size | 10 | Explain how the study size was arrived at | 17 |
| Quantitative variables | 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why | 17 |
| Statistical methods | 12 | (*a*) Describe all statistical methods, including those used to control for confounding | 17 |
| | | (*b*) Describe any methods used to examine subgroups and interactions | 17 |
| | | (*c*) Explain how missing data were addressed | NA |
| | | (*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed<br>*Case-control study*—If applicable, explain how matching of cases and controls was addressed | 17 |

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|---|---|---|---|
| | | *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy | |
| | | (*e*) Describe any sensitivity analyses | NA |
| **Results** | | | |
| Participants | 13* | (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed | NA |
| | | (b) Give reasons for non-participation at each stage | NA |
| | | (c) Consider use of a flow diagram | NA |
| Descriptive data | 14* | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders | NA |
| | | (b) Indicate number of participants with missing data for each variable of interest | NA |
| | | (c) *Cohort study*—Summarise follow-up time (eg, average and total amount) | NA |
| Outcome data | 15* | *Cohort study*—Report numbers of outcome events or summary measures over time | NA |
| | | *Case-control study*—Report numbers in each exposure category, or summary measures of exposure | NA |
| | | *Cross-sectional study*—Report numbers of outcome events or summary measures | NA |
| Main results | 16 | (*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included | NA |
| | | (*b*) Report category boundaries when continuous variables were categorized | NA |
| | | (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period | NA |
| Other analyses | 17 | Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses | NA |
| **Discussion** | | | |
| Key results | 18 | Summarise key results with reference to study objectives | NA |
| Limitations | 19 | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias | 19 |
| Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence | NA |
| Generalisability | 21 | Discuss the generalisability (external validity) of the study results | NA |
| **Other information** | | | |
| Funding | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based | 21 |

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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# National, clinical cohort study of late effects among survivors of acute lymphoblastic leukemia: the ALL-STAR study protocol.



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# National, clinical cohort study of late effects among survivors of acute lymphoblastic leukemia: the ALL-STAR study protocol.

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**ABSTRACT**

**Introduction:** More than 90% of patients diagnosed with childhood acute lymphoblastic leukemia (ALL) today will survive. However, half of survivors are expected to experience therapy-related chronic or late occurring adverse effects, reducing quality of life. Insight into underlying risk trajectories is warranted. The aim of this study is to establish a Nordic, national childhood ALL survivor cohort, to be investigated for the total somatic and psychosocial treatment-related burden as well as associated risk factors, allowing subsequent linkage to nation-wide public health registers.

**Methods and analysis:** This population-based observational cohort study includes clinical follow-up of a childhood ALL survivor cohort (N=475), treated according to a common Nordic ALL protocol during 2008-2018 in Denmark. The study includes matched controls. Primary endpoints are the cumulative incidence and cumulative burden of 197 health conditions, assessed through self- and proxy-report questionnaires, medical chart validation, and clinical examinations. Secondary endpoints include organ-specific outcome including cardiovascular and pulmonary function, physical performance, neuropathy, metabolic disturbances, hepatic and pancreatic function, bone health, oral and dental health, kidney function, puberty and fertility, fatigue, and psychosocial outcome. Therapy exposure, acute toxicities and host genome variants are explored as risk factors.

**Ethics and dissemination:** The study is approved by the Regional Ethics Committee for the Capital Region in Denmark (H-18035090/H-20006359) and by the Danish Data Protection Agency (VD-2018-519). Results will be published in peer-reviewed journals and are expected to guide interventions that will ameliorate the burden of therapy without compromising chance of cure.



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**STRENGTHS AND LIMITATIONS OF THIS STUDY**

- The first population-based, uniformly treated, Nordic childhood and young adult ALL survivor cohort to be systematically evaluated for treatment-related organ-wide morbidity and psychosocial impact, thus supplementing National public demographic, socio-economic and health registries.
- Additional strengths include use of matched controls, systematic subjective and objective assessments of outcome and alignment of adverse effects definitions with established classification systems.
- Estimation of the cumulative burden includes both persistent and recurrent events, thereby describing the total disease burden more comprehensively than traditional measures such as cumulative incidence.
- Initial cross-sectional analyses are limited by a follow-up of 3.5-14 years, acknowledging that the full burden of ALL and leukemic therapy may not yet have emerged.
- Self-report and systematic clinical data will supplement data from the Danish Nation-wide public demographic, socio-economic and health registries.

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## 1. INTRODUCTION

Five-year overall survival rates for childhood acute lymphoblastic leukemia (ALL) has climbed from less than 10% to above 90% during the last seven decades as a result of chemotherapy intensification, refined risk stratification, and improved supportive care.[1–3] However, cure comes at a cost.[4] All patients experience acute but transient toxicities during therapy (e.g. infections, mucositis and peripheral neuropathy), and half of patients are burdened by at least one severe, potentially life-threatening organ toxicity such as acute pancreatitis, thromboembolism, or severe neurotoxicity.[5–8] Acute organ damage resulting from leukemia and/or therapy may persist (e.g. insulin dependent diabetes[9]) or emerge (e.g. osteonecrosis[10]) several years into survival as late effects. The 30-year old survivor will have experienced an average of 5.4 health conditions, and half of survivors face at least one chronic health condition 20 years from ALL diagnosis, both measures significantly exceeding those among siblings and community controls.[11,12] This disproportion in morbidity rate seems to amplify with increasing age.[12] Certain therapeutic exposures have been reduced over time (e.g. reduction in cardiotoxic anthracycline exposure and limited use of cranial irradiation in first-line therapy protocols),[13,14] which has decreased risk of early mortality and lowered the prevalence of treatment-related cancers, severe cognitive deficits, hypothalamic-pituitary dysfunction, and immunological disease.[12,14] However, the number of health conditions per individual survivor is still double that in controls and now mainly include endocrine system disorders, musculoskeletal-, neurological-, and cardiovascular conditions,[12] maintaining risk of impaired physical, cognitive, and emotional function, socioeconomic achievements, and health-related quality of life.[11,15–18] Therapy exposure and genetic susceptibility are considered the two major risk factors predicting late morbidity.[19] Risk of specific late effects are associated with cumulative chemotherapy exposures,[20–29] but no safe lower doses have been established. Specific genetic variants have been linked with survivor obesity, reduced bone mineral density, cardiotoxicity, skeletal muscle dysfunction, and neurocognitive dysfunction,[30–33] however, clinical recommendations await harmonization of outcomes, larger sample sizes, and replication in independent cohorts.[30] To date, many late effects studies are observational and focus on one or few organ systems, cross-sectional in design, or emerge from single centers with resulting risk of selection bias and limited sample power. A few very large (>10,000 patients), multi-institutional childhood cancer survivor cohort studies exist, such as the US Childhood Cancer Survivor Study,[34] the Nordic Adult Life after Childhood Cancer in Scandinavia study,[35] and the British Childhood Cancer Survivor Study[36]. Most studies emerging from these cohorts rely on self-reported and register-based data, while few include



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systematic clinical data, none of which include Nordic survivors.[37]

During the 10-year period 2008-2018, patients diagnosed with Philadelphia-chromosome negative ALL at age 1–45 years in the Nordic and Baltic countries, have been treated according to the Nordic Society of Pediatric Hematology and Oncology (NOPHO) ALL2008 protocol described elsewhere.[3,5,38] Two thirds of this cohort were below 18 years of age at diagnosis. The aim of the Acute Lymphoblastic Survivor Toxicity And Rehabilitation (ALL-STAR) study is to establish a national, Danish NOPHO ALL2008 survivor cohort, to be assessed for the total somatic and psychosocial treatment-related burden, using both self-report and systematic clinical data that will supplement data from the Danish Nation-wide public demographic, socio-economic and health registries.[39]

## 2. METHODS

### Study aims

*Primary aim*

To quantify the burden of health conditions occurring during the first decade of survivorship among survivors of childhood and young adult ALL.

*Secondary aims*

To describe, in detail, organ-specific health among survivors as compared to matched controls and normative data; and to investigate host genome variants, therapy exposure, and acute toxicities as risk factors for organ-specific late effects and for the overall cumulative burden. Furthermore, to establish a platform for life-long follow-up in this survivor cohort, facilitating longitudinal studies and linkage to Nation-wide public, socio-economic and health registries.

### Study design

The ALL-STAR study is a national, Danish, population-based, observational cohort study, including prospective clinical follow-up in a retrospective childhood and young adult ALL survivor cohort. This present protocol primarily focuses on the initial, cross-sectional phase of the project.



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**Participants**

*Study population*

All survivors treated in Denmark according to the NOPHO ALL2008 protocol and minimum one year from therapy cessation (3.5 years from ALL diagnosis) are eligible. This corresponds to all patients (N=475) aged 1–45 years at diagnosis with Ph$^-$ B-cell precursor or T-cell ALL, diagnosed between July 2008 and October 2018 (the complete NOPHO All2008 protocol period). A control group consisting of age- and sex-matched individuals (1:1) is recruited for the study. First degree relatives to survivors and individuals with previous or ongoing cancer, previous or ongoing chemotherapy and/or previous or ongoing radiation therapy are excluded as controls. Study recruitment for the initial cross-sectional studies opened in February 2019 and will terminate in September 2022, allowing for the entire survivor cohort to meet inclusion criteria.

*Recruitment*

Eligible survivors are identified through the NOPHO ALL2008 registry. Contact information is obtained through medical charts and provided by treating physicians to the research team. Written information is sent to parents if survivor age is < 15 (addressed at survivor and parents), to parents and the survivor if aged 15–17.9, and to survivors aged ≥ 18 years. Contact is obtained through subsequent phone calls. All survivors and/or families are invited to an on-site meeting for further information before consent. Controls are recruited via participating survivors (or parents) who appoint and invite friends or relatives to participate. Potential controls (or parents) contact the research team, with subsequent written and oral information provided as described for survivors, before possible consent.

**Endpoints**

*Primary endpoints and hypothesis*

The two primary endpoints are cumulative incidence and cumulative burden of 197 health conditions presented in Table 1.



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**Table 1. Health conditions investigated in the ALL-STAR study**

| AUDITORY-HEARING | GASTROINTESTINAL | INFECTIONS | NEUROLOGIC | PULMONARY |
|---|---|---|---|---|
| Cholesteatoma | Bowel perforation | Bronchial/lung infection C/R | Autonomic dysfunction | Asthma |
| Hearing loss | Celiac disease | Endocarditis | Cavernoma | COPD |
| Tinnitus | Constipation | Gastrointestinal infection | Cerebellar dysfunction | Epistaxis, chronic/recurrent |
| Vertigo | Dysphagia | Genitourinary infection | Cerebral necrosis | Obstructive sleep apnea |
| | Enterocolitis | Hepatitis B, chronic | Cerebrovascular accident | Obstructive ventilatory defect |
| **CARDIOVASCULAR** | Esophageal varices | Hepatitis C, chronic | Cerebrovascular disease | Pleural space disorders |
| Aortic root aneurysm | Esophagitis | HIV infection | Cranial nerve disorder | Pneumonitis |
| Arteriovenous malformation | Fecal incontinence | Lymphatic infection | Dysarthria | Pulmonary diffusion defect |
| Atrioventricular heart block | Gastritis/duodenitis | Meningoencephalitis | Generalized muscle weakness | Pulmonary embolism |
| Bradycardia, sinus | GERD | Osteomyelitis | Headaches, chronic/ recurrent | Respiratory tract hemorrhage |
| Cardiopulm. fitness, reduced | Gastrointestinal fistulas | Otitis media, C/R | Hydrocephalus | Restrictive ventilatory defect |
| Conduction abnormalities | Gastrointestinal hemorrhage | Pelvic inflammatory disease | Hydrosyringomyelia | Tracheal aspiration |
| Congestive heart failure | Gastrointestinal necrosis | Pharyngitis/tonsillitis, C/R | Intracranial hemorrhage | Tracheal stenosis |
| Coronary artery disease | Gastrointestinal obstruction | Sinusitis, C/R | Movement disorders | |
| Cor pulmonale | Gastrointestinal strictures | Soft tissue infection | Multiple sclerosis | **PSYCHIATRIC** |
| Dysrhythmia | Gastrointestinal ulcer | | Narcolepsy | Anxiety |
| Heart valve disorder | Gastroparesis syndrome | **MUSCULOSKELETAL** | Nerve root disorder | Depression |
| High total cholesterol | Malabsorption syndrome | Amputation | Neurogenic bladder | Other psychiatric disorders |
| Hypertension | Pancreatic insufficiency | Arthralgia | Neurogenic bowel | |
| Hypertriglyceridemia | Pancreatitis | Arthritis | Neuromuscular disorders | **RENAL / URINARY** |
| LV systolic dysfunction | Proctitis | Bone mineral density deficit | Paralytic disorder | Acute kidney injury |
| Pericarditis | | Hernia | Peripheral motor neuropathy | Chronic hematuria |
| Prolonged (QTc) interval | **HEPATOBILIARY** | Intervertebral disc disorder | Peripheral sensory neuropathy | Chronic kidney disease |
| Pulmonary hypertension | Cholecystitis/Cholelithiasis | Kyphosis | Pseudomeningocele | Incontinence |
| Raynaud phenomenon | Fibrosis/Cirrhosis | Limb length discrepancy | Pseudotumor cerebri | Obstructive uropathy |
| RV systolic dysfunction | Hepatic failure | Osteonecrosis | Seizures | Urinary bladder dysfunction |
| Tachycardia, sinus | Hepatopathy | Palatal defects, acquired | | Urinary tract calculi |
| Thromboembolic event | Portal hypertension | Scoliosis | **OCULAR/VISUAL** | Vesicoureteral reflux, acquired |
| Vascular disease | Veno-occlusive disease | Skeletal spine disorder | Cataract | |
| | | Slipped capital femoral epiphysis | Diplopia | **REPRODUCTIVE / GENITAL** |
| **ENDOCRINE** | **HEMATOLOGIC** | | Dry eye syndrome | Abnormal sperm concentration |
| Abnormal glucose metabolism | Anemia | **ORAL / DENTAL** | Eyelid function disorder | Cervical dysplasia |
| Adrenal insufficiency | Coagulopathy | Dental caries | Glaucoma | Dysfunctional uterine bleeding |
| Adult GH deficiency | Iron overload | Dental erosion | Ocular disease, noninfectious | Endometriosis |
| Childhood GH deficiency | Neutropenia | Gingivitis | Ocular surface disease | Erectile dysfunction |
| Diabetes insipidus | Polycythemia | Periodontitis | Photophobia | Genitourinary adhesions |
| GH excess | Thrombocytopenia | Sialadenitis, acute | Phthisis bulbi | Hypogonadism, central |
| Hyperparathyroidism | Thrombocytosis | Sialadenitis, chronic | Retinal detachment | Leydig cell insufficiency |
| Hyperprolactinemia | | Salivary gland dysfunction | Retinopathy | Polycystic ovarian syndrome |
| Hyperthyroidism | **IMMUNOLOGIC** | TMJ disorder | Strabismus | Precocious puberty |
| Hypoparathyroidism | Autoimmune disorders | Dental maldevelopment | Visual acuity, reduced (OD) | Primary ovarian failure |
| Hypothyroidism | Graft-versus-host disease | | Visual acuity, reduced (OS) | Prostatic hypertrophy, benign |
| Overweight/Obesity | Immunodeficiency | **NEOPLASMS** | Visual field deficit | Vaginal fistula |
| Sarcopenic obesity | | Benign neoplasms | | Vaginal stenosis |
| SIADH | | Malignant neoplasms | | |
| Underweight | | | | |

Abbreviations: Cardiopulm. Fitness, red. = cardiopulmonary fitness, reduced; COPD = Chronic obstructive pulmonary disease; CR = chronic/recurrent, GERD = gastroesophageal reflux disease; GH = growth hormone; LV = left ventricle; RV = right ventricle; SIADH = syndrome of inappropriate antidiuretic hormone secretion; TMJ = temporomandibular joint; QTc = corrected QT interval



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We hypothesize that the cumulative incidence and cumulative burden are significantly higher among survivors of childhood and young adult ALL already during the first decade of survival, when compared with sex- and age- matched controls and normative data.

The measure of cumulative burden considers occurrence of multiple health conditions and recurrent events, thereby encompassing the total disease burden more comprehensively than cumulative incidence which includes only first occurrence of an event.[40,41] The 197 conditions investigated in the ALL-STAR study are defined and graded according to the St Jude Children's Research Hospital modification of the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE; version 4.03),[42] developed to optimize characterization of long-term and late-onset health conditions among childhood cancer survivors.[43] Ten additional health conditions (generalized muscle weakness, reduced cardiopulmonary fitness, sarcopenic obesity, and seven oral/dental conditions) have been added. Definitions and grading criteria for all conditions are provided in Supplementary Table 1.

*Secondary endpoints*

Secondary endpoints include 1) organ-specific outcome including metabolic syndrome and body composition, hepatic function, pancreatic function, bone health, cardiac function, pulmonary function, peripheral- and autonomic neuropathy, physical performance, kidney function, pubertal timing, fertility, oral and dental health and 2) psychosocial outcome including emotional distress, fatigue, and health-related quality of life.

An overview of the ALL-STAR study is provided in Figure 1.

**Data collection**

Data are collected through questionnaires and clinical evaluations. An overview of ALL-STAR source data used for evaluation of the 197 health conditions is provided in Supplementary Table 1.

Questionnaire data

An electronic questionnaire is sent to participants prior to clinical examinations. The questionnaire is adjusted according to self-report (age ≥ 15 years), proxy-report (age < 18), age, sex, and status as survivor or control. Items include demographics, use of health care services, medicine and nutritional supplements, medical history (including age at the onset of a confirmed condition), pubertal status and fertility, familial dispositions, health behavior, mental



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health, quality of life, and socioeconomic status. An overview of questionnaire versions and content is provided in Supplementary Table 2.

Clinical data

All clinical examinations are performed at either Copenhagen University Hospital or Aarhus University Hospital, as requested by the participant. Examinations are performed during 10 hours in a single day. The examination program and description of clinical investigators are provided in Supplementary Table 3.

*Evaluation of metabolic syndrome and body composition*

Endpoints include metabolic syndrome (MetS), insulin sensitivity, lipid profile, abdominal circumference, body mass index (BMI) for adults and BMI standard deviation scores for children, based on national reference material,[44,45] lean body mass and fat mass. Adult MetS is defined according to the *National Cholesterol Education Program Adult Treatment Panel* criteria,[46] and includes central obesity, dyslipidemia, hypertension, and elevated fasting glucose. Pediatric MetS is defined using the same measures.[47] Questionnaire items include metabolic disease and family disposition, prescription medicine, nutritional supplements, and lifestyle (diet, level of physical activity and sedentary behavior). Clinical investigations include anthropometrics (weight, height and abdominal circumference) and blood pressure (described in cardiovascular section). Fasting blood samples include glucose, glycated hemoglobin, insulin, pro-insulin c-peptide, total cholesterol, high density lipoprotein cholesterol, low-density lipoprotein cholesterol, very low-density lipoprotein cholesterol, triglycerides, glucagon, and leptin. Homeostatic Model Assessment for Insulin resistance score is calculated as fasting plasma glucose (mmol/L) x fasting plasma insulin (microU/L)/22.5.[48] Body composition (fat and lean body mass and android/gynoid fat distribution) is assessed with dual-energy X-ray absorptiometry (DXA) (Lunar Prodigy, GE Healthcare, WI, USA; or Hologic Horizon A, Hologic, Marlborough, MA, USA), and is adjusted for sex and pubertal stage.

*Evaluation of hepatic function and gallbladder*

Endpoints include signs of hepatocellular damage, impaired liver synthesis, iron overload, hepatic fibrosis, portal hypertension, and gall bladder disease (cholestasis, cholangitis, cholelithiasis). Questionnaire items include symptoms of hepatic disease (fatigue, abdominal pain, nausea, jaundice, discolored urine, itchy skin), hepatic diagnoses, alcohol consumption and use of prescription medicine. Fasting blood samples include alanine transaminase, aspartate



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transaminase, alkaline phosphatase, gamma-glutamyl transferase, bilirubin, lactate dehydrogenase, prothrombin time, international normalized ratio, albumin, ferritin, transferrin saturation, alfa-1 antitrypsin, platelets and immunoglobulins. Serum is stored for evaluation of viral antibodies (Hepatitis A, B, C, Cytomegalovirus and Epstein-Barr virus) in case of elevated transaminases. Hepatic ultrasound is performed using a convex, abdominal probe (C1-5, GE Logiq E9 or E10, GE Healthcare, Chicago, USA). The liver, gallbladder, gall ducts, liver artery and spleen are evaluated for appearance and size. Portal vein flow is measured using Doppler. Ultrasound 2D shear wave elastography is performed on the right liver lobe for evaluation of parenchymal stiffness and fibrosis.[49]

*Evaluation of pancreatic function*

Endpoints include pancreatic disease, endocrine and exocrine function, and morphological appearance. Questionnaire items include pancreatic symptoms and disease, diet and alcohol consumption. Fasting blood samples include pancreatic amylase, lipase, glucose, glycosylated hemoglobin, insulin, and proinsulin c-peptide. Fecal elastase-1 is evaluated in survivors only and associated with occurrence of asparaginase-associated pancreatitis during ALL therapy. Pancreatic ultrasound is performed using a convex, abdominal probe (C1-5, GE Logiq E9 or E10, GE Healthcare, Chicago, USA) for anterior-posterior measurement of caput and corpus, and for evaluation of morphological changes (tumor, inflammation, edema, pseudocysts, and ductal ectasia).

*Evaluation of bone mineral density*

Endpoints include bone mineral density (BMD), bone fractures, and biomarkers of bone metabolism. Questionnaire items include bone- and joint symptoms, history of fractures and low BMD, age of menarche, hormone supplements, calcium and vitamin D intake, and family history of bone disease. Biomarkers include ionized calcium, phosphate, alkaline phosphatase, parathyroid hormone, and 25-OH-vitamin D. Bone mineral content, bone area, and BMD is determined by DXA (Lunar Prodigy, GE Healthcare, WI, USA; or Hologic Horizon A, Hologic, Marlborough, MA, USA) total body, lumbar spine (L1-L4), and dual-femur scans. Adult bone mineral values are analyzed as age- and sex-specific standard deviations and expressed as z- and T-scores. Pediatric bone mineral values are analyzed as age- and sex-specific standard deviations and expressed as z-scores. All pediatric bone mineral values are corrected for height.

*Evaluation of cardiovascular function*

Endpoints include left and right ventricular systolic and diastolic dysfunction, ventricular volumes and left ventricular mass, myocardial fibrosis, myocardial iron deposits, atrial thrombosis, conduction abnormalities and hypertension.



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Questionnaire items include cardiovascular symptoms, diagnoses, prescription medicine, and familial disposition to cardiovascular disease. Automated oscillometric blood pressure is measured in all, and manual auscultatory systolic blood pressure is measured in children (< 18 years). Cardiac biomarkers include N-terminal pro b-type natriuretic peptide and troponin-T. Cardiac electrical activity is assessed with a 12-lead electrocardiogram (ECG). Imaging includes speckle tracking echocardiography and cardiac magnetic resonance imaging (MRI). Echocardiography is performed using a Vivid E95 ultrasound scanner (GE Healthcare Vingmed Ultrasound AS, Horten, Norway) to obtain measurements of left ventricular output and volumes, as well as global longitudinal systolic strain. An intravenous contrast agent (SonoVue®) is used to improve imaging.[50] Cardiac MRI is performed using a whole body 1.5T scanner for assessment of left ventricular systolic function, volumes, and mass. Multiparametric characterization including T1, T2, T2*and mapping is performed for visualization of possible myocardial edema and fibrosis, and to evaluate myocardial iron content.[51,52] Intravenous gadolinium-containing contrast (0,15 mmol/kg Gadovist®) is used for assessment of extracellular volume fraction in survivors (not controls).

*Evaluation of pulmonary function*

Endpoints include function of conductive and acinar airways, resistance of airways, alveolar volumes, alveolar membrane diffusion, lung clearance index, capillary volume, total diffusion capacity, spirometric volumes and flows, and reversibility. Questionnaire items include respiratory symptoms, pulmonary diagnoses, smoking and use of prescription medicine. Prebronchodilator and postbronchodilator spirometry is performed using a Jaeger MasterScreen Bodybox and Jaeger Vyntus Spiro (CareFusion, Hochberg, DE; Vyaire Medical, Bayern, DE) for measurement of forced expiratory volume during the first second, forced vital capacity (FVC), and forced expiratory flow between 25% and 75% of FVC. Impulse oscillometry including reversibility test is performed at University Hospital of Aarhus using a Jaeger MasterSceen Bodybox and Jaeger Vyntus IOS system (CareFusion, Hochberg, DE; Vyaire Medical, Bayern, DE) to evaluate lung volumes, resistance and elasticity of the lung. Nitrogen multiple breath washout is performed using an Ecomedics Exhalyzer D, N2 and SF6 option (Ecomedics, Dürnten, CH) to assess Lung Clearance Index including indexes of acinar and conductive airways ventilation heterogeneity. Single breath diffusion capacity for carbon monoxide and nitrogen oxide, corrected for hemoglobin, is performed using a Jaeger Vyntus Body (CareFusion, Hochberg, DE) for real time Single Breath diffusion to evaluate diffusion membrane capacity and



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pulmonary capillary volume. All pulmonary measures are compared with normative data[53–58] and with data from the matched controls.

*Evaluation of peripheral and autonomic neuropathy*

Endpoints include sensory-, motor-, and autonomic nerve dysfunction. Peripheral neuropathy is assessed according to recommendations from *American Academy of Neurology, the American Association of Electrodiagnostic Medicine* and *American Academy of Physical Medicine and Rehabilitation,*[59] and using the Total Neuropathy Score, which includes self-report of sensory, motor and autonomic symptoms, pin sensibility, vibration sensibility (quantitative threshold using Vibrameter® type IV (SOMEDIC Electronics, Solna, Sweden) and Biothesiometer® model PVD-LP (Bio Medical Instruments company, Ohio, USA)), muscle strength (Medical Research Council 5-grade score), deep tendon reflexes and amplitude of sural and peroneal nerves.[60] Abnormal values corresponding to quantitative vibration threshold are calculated as percentages relative to the upper limit of normal values based on data from matched ALL-STAR controls and previously published normative data.[61–63] Electroneurography is performed using standard surface recording techniques (Neuroline 715, Ambu®). A G3 Keypoint platform (DanTec, Natus, USA) is used for amplification, filtration and storing of signals (motor: 2Hz-10kHz; sensory: 20Hz-10kHz). Electroneurography includes unilateral evaluation of Sensory Nerve Action Potential from the sural nerve, compound Motor Action Potential from the peroneal nerve, the distal motor latency in the peroneal nerve and both sensory and motor nerve conduction velocities. Recorded values are compared with ALL-STAR control values and with unpublished national, Danish age- and gender-specific reference values, and reported as standard deviations from the expected mean (z-scores). Autonomic neuropathy is evaluated with the validated 31-item composite autonomic symptom questionnaire, COMPASS 31[64,65], which assesses orthostatic intolerance, vasomotor, secretomotor, gastrointestinal, bladder and pupillomotor function. Objective evaluation of autonomic dysfunction is performed by analysis of heart rate variability (HRV) obtained from a 21-minute Holter recording (13 minutes reclined resting period followed by shift to standing position with continued ECG recording for eight minutes). The RR-interval dataset derived from the ECG segments is analyzed for heartrate and HRV. Analysis of HRV is performed in both the time and frequency domain and changes elicited by the standing position is calculated.

*Evaluation of physical performance*

Endpoints include cardiorespiratory fitness, level of physical activity, physical function and muscle strength.



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Questionnaire items include levels of sedentary behavior and of physical activity, which is objectified with a 7-day continuous accelerometer measurement (ActiGraph™ model GT3X+, ActiGraph LLC, Pensacola FL, USA). Cardiorespiratory fitness is evaluated using an electronically braked cycle ergometer (Lode Corival Pediatric or Monark Ergomedic 839 E) following a modified Godfrey protocol.[66,67] Ventilation and gas exchange data are determined breath-by-breath (INNOCOR ergo-spirometry-system, INNO00010, Innovision, DK-5260 Odense, Denmark or Jaeger Master Screen® Vyntus CPX and JLAB Software Package™). Peak oxygen uptake ($VO_2$peak) is defined as the highest mean over 60 seconds. Results are reported as standard deviations from the expected mean (z-scores), derived from the age- and sex-matched ALL-STAR controls. Muscle strength is evaluated as isometric muscle strength (knee extensor, upper body (Gym 2000) with a Strain gauge (US2A100 kg, Holtinger, Germany) and custom-made amplifier), and handgrip strength (Saehan hand dynamometer, Glanford Electronics, Scunthorpe). Dynamic muscle strength is evaluated by the counter movement jump test (FP4, HUR-Labs Oy, Tampere, Finland) and physical function (Sit-to-stand 30s and 60s[68], Timed-Up-and-Go[69]).

*Evaluation of kidney function*

Endpoints include kidney function and kidney size. Questionnaire items include urinary tract symptoms and disease and use of prescription medicine. Fasting blood-samples include creatinine, urea, cystatin-c, sodium, potassium, phosphate, albumin, ionized calcium, and parathyroid hormone. Estimated glomerular filtration rate is evaluated using creatinine in adults,[70] and using creatinine, urea and cystatin-C in children[71]. Proteinuria is determined by the albumin-creatinine ratio in a morning urine specimen. A spot urine dip stick test is performed to evaluate hematuria and urine pH. Kidney size is evaluated by ultrasonography (convex, abdominal probe (C1-5), GE Logiq E9 or E10, GE Healthcare, Chicago, USA) as longitudinal anterior-posterior length, width and cross-sectional ap-length, and abnormal appearance (e.g. hydronephrosis, cysts or tumors) is registered. Kidney size is related to body weight, height and lean mass.

*Evaluation of pubertal status and gonadal function*

Pubertal stage is evaluated in all participants aged > 8 years at time of evaluation. Endpoints include age at menarche/spermarche, pubertal stage, and levels of reproductive hormones. Questionnaire items include age at menarche and use of contraception for females, age at spermarche for males, and hormonal substitution. Pubertal stage is evaluated according to Tanner[72] in combination with testicular volume for males, estimated by comparative



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palpation using a Prader orchidometer[73]. Results are compared with Danish puberty normograms.[74,75] Measurements of serum follicle stimulating hormone, luteinizing hormone, estradiol, testosterone, insulin-like peptide 3, inhibin B, anti-müllerian hormone, and sex hormone binding globulin are performed and levels are compared with sex-, and age matched national reference material as well as with ALL-STAR controls.

*Evaluation of fertility*

Fertility is evaluated in all participants aged ≥ 18 years. Endpoints include impaired fertility (defined as previously diagnosed impaired fertility or infertility and/or use of assisted reproductive technology), number and health of offspring. Questionnaire data include items regarding health behavior, previous relationship/marital status, attempts to conceive, menopause, results from fertility investigations, natural conceptions, use of assisted reproductive technology, pregnancies, miscarriages, voluntary terminations, stillbirths, livebirths, and health of offspring. Reproductive hormones and testicular volume are assessed as described in the previous section.

*Evaluation of oral health and salivary secretion*

Oral health assessments are performed at the Copenhagen University Hospital. Endpoints include oral symptoms, impaired oral and dental health (mucosal changes, caries, erosions, gingivitis, periodontitis, malocclusions, temporomandibular dysfunction and salivary gland dysfunction) and changes in salivary microbiome and proteome. Questionnaire items include oral symptoms, current medication, dietary supplements, tobacco and alcohol consumption and oral hygiene habits. Xerostomia is assessed by means of the Bother Index[76], Xerostomia Inventory-8[77] and visual analogue scale (0-10)[78]. Additional evaluation of the oral health includes a clinical examination with palpation of the temporomandibular joint, salivary glands and regional lymph nodes; assessments of the morphological and functional occlusion, dental status (Decayed Missing Filled Teeth scores, dental erosion scores, dental malformations, delayed eruptions), periodontal status (gingival inflammation and dental plaque indices and assessment of periodontal probing depth) and mucosal status (mucosal changes and signs of dryness using Clinical Oral Dryness Score[79]). Unstimulated and chewing-stimulated whole saliva flow rates are measured according to the drooling method.[80] DNA is extracted from the saliva samples and the microbiome characterized by *HOMINGS* (Human Oral Microbe Identification using Next Generation Sequencing) with bacterial species-level identification based on 16S rDNA comparisons. Salivary proteome analyses are performed by means of 2-dimensional electrophoresis (2DE) and



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MALDI-TOF-MS (Matrix-Assisted Laser Desorption/Ionization Time-of-phFlight Mass Spectrometry). Western blot analysis and ELISA are used for validation of the 2DE results.

*Evaluation of other somatic health conditions*

Iron overload is evaluated with plasma levels of ferritin and transferrin saturation and with cardiac MRI T2* mapping. Hyper- and hypothyroidism is investigated with questionnaire data and measurement of thyroid stimulating hormone and free thyroxine. Hyperparathyroidism is evaluated with parathyroid hormone and total and ionized calcium. Additional health conditions specified in Table 1, but not described above, are evaluated using questionnaire data and medical chart validation as reported in Supplementary Table 1.

*Evaluation of mental health and quality of life*

Endpoints include psychiatric disease, social relations, emotional distress (anxiety, depression, and fatigue), executive function, and health-related quality of life. Questionnaire items include psychiatric diagnoses and psychopharmaceuticals. Additional psychosocial data are collected via instruments from Pediatric Quality of Life Inventory® (PedsQL), Patient Reported Outcomes Measurement Information System®(PROMIS), and the Behavior Rating Inventory of executive Function® (BRIEF) system. Specific instruments and versions are provided in Supplementary Table 4.

**Use of previously collected data for risk factor analysis**

ALL patient characteristics (date of diagnosis, tumor burden, immunophenotype, cytogenetics, minimal residual disease levels, final risk stratification, participation in protocol randomizations, and occurrence of 19 well-defined acute toxicities) are obtained from the NOPHO ALL2008 registry.[38] Medical chart data are used for validation of registered acute toxicities and for validation of self-reported health conditions (including dates). Genotyping for genome wide association studies (GWAS) has been performed previously on germline DNA from samples obtained after clinical remission using the exome-enriched Illumina Infinium Omni2.5exome-8- BeadChip arrays and is available for approximately 70% of the survivor population. Whole blood samples are collected from participants (including controls) not previously genotyped and samples are analyzed using the same platform.



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**Data management**

Study data were collected and managed using Research Electronic Data Capture (REDCap) tools hosted at Copenhagen University Hospital.[81,82] REDCap is a secure, web-based software platform designed to support data capture for research studies, providing 1) an intuitive interface for validated data capture; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for data integration and interoperability with external sources.

**Statistical considerations**

Cumulative incidence of the 197 health-conditions is calculated (individually and grouped according to organ system and severity grade) for survivors and controls and presented with 95% confidence intervals. Gray's test is used for comparison between the two groups. Cumulative burden of the 197 health-conditions is calculated (individually and grouped according to organ system and severity grades) in survivors and controls by the method of mean cumulative count, estimating the mean number of recurring or multiple health events in the presence of competing risk[83], and presented with 95% confidence intervals. For this purpose, health-conditions are categorized pre-analysis into three subtypes (chronic, non-recurrent; single, recurrent; and chronic, recurrent) based on clinical definitions of recurrence and chronicity, as described by others.[40] Based on a projected sample size of 250 survivors and 250 controls (survival rate of 90% in the Danish NOPHO ALL2008 patient cohort and a conservative recruitment rate of 60%), a 16% prevalence of chronic disease among Danish children[84], and significance level alpha=0.05, we will have a power of 87% to detect a hazard ratio (HR) of 2.0 in a Cox regression model, which is the lowest HR previously reported in a study comparing leukemia survivors with sibling controls.[85] Secondary outcomes (i.e. description of organ-specific functions) are compared between survivors and controls using relevant regression models (e.g. linear regression models, logistic regression models, or Cox regression models). For survivors, associations of primary and secondary outcomes with therapy exposure and occurrence of acute toxicities are explored using multiple regression models. Association with single nucleotide polymorphisms (SNP) is explored with genome-wide association analysis and using a candidate gene approach where relevant SNPs have been identified. Differences in demographics between survivor participants and non-participants are explored using Fischer's exact test for binary data and Student's/Welch's t-test or Wilcoxon rank sum test.



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**Patient and Public Involvement**

In preparation of this study, we performed a qualitative interview study among adolescent and young adult NOPHO ALL2008 survivors to identify the challenges they perceive as most important.[18] Results from this study have been incorporated into the ALL-STAR examination program, securing focus on the issues most important to the survivors.

**Longitudinal follow-up.**

The cohort is invited for follow-up examinations corresponding to five-year intervals from diagnosis, thereby aligning survival time at data capture. Results from the initial cross-sectional studies will inform which examinations to prioritize and additional endpoints can be added to address new hypotheses. The ALL-STAR database will facilitate repeated invitations and longitudinal data capture. Participants will provide new informed consent before repeated examinations.

## 3. ETHICS AND DISSEMINATION

The study has been approved by the Regional Ethics Committee for the Capital Region in Denmark (no. H-18035090 and H-20006359), the Danish Data Protection Agency (no. VD-2018-519) and is conducted in accordance with the Helsinki Declaration. Written informed consent is obtained from all participants prior to enrollment. All participants can choose to participate in only parts of the study, can choose not to be informed of results, and can withdraw consent at any time. Study results will be published in international peer-reviewed scientific journals and presented at relevant conferences.

## 4. DISCUSSION

The ALL-STAR cohort is the first Nordic, population-based childhood and young adult ALL survivor cohort treated according to the same ALL protocol, to be uniformly evaluated for treatment-related morbidity across several organ systems, using both self-report data and objective, clinical investigations.

The evolution of long-term, adverse consequences of antileukemic therapy is complex and dependent not only on therapy exposure and genetic susceptibility, but also on age at diagnosis, preexisting morbidity, individual resources, resources among family and peers, and on surrounding health care- and societal structures. The comparison of a



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Nordic survivor cohort with survivor cohorts from other western countries will provide insight into the consequences of differing systems, as well as differences in treatment regimens used. Scandinavian countries, and particularly Denmark, have access to extensive register data including health- and socioeconomic information, linked to the individual person and surrounding network through personal identification numbers.[39] Coupling of systematic survivor data obtained in the ALL-STAR study to national register data will enable contextualizing association studies novel to survivorship research.

Strengths of the ALL-STAR study include a population-based design, a homogenous and well characterized cohort, the combination of both subjective and objective assessments of outcome, and inclusion of matched controls. The ALL-STAR cohort has already been characterized by prospective registration of tumor burden, immunophenotype, cytogenetics, treatment response, and occurrence of 19 severe toxicities, performed by treating physicians from time of diagnosis until end of therapy.[38] These data enable high precision evaluation of risk factors and confounders associated with our main outcome of interest. Similarly, high quality survivor data is secured through self-report data, medical chart validation, and systematic clinical examinations across most organ systems and using both well-established and novel, advanced techniques. This combination of data enables inclusion of survivor perspective while minimizing risk of recall bias and inaccurate information. Furthermore, the systematic screening of organ functions facilitates capture of low-grade conditions, which are likely to be underestimated if using retrospective or self-report data only.[40] Since the investigated health conditions are not pathognomic, the inclusion of matched controls, often missing in survivorship studies, will support conclusions made regarding the risk patterns which we seek to identify.

Despite vast amounts of late effects research being performed, no international consensus on how to characterize therapy-related late effects exist currently. Lack of precise definitions and uniform grading result in substantial variability across studies, hindering meaningful pooling and comparisons of results.[86] Cancer and therapy-related acute toxicities are traditionally defined and graded according to the CTCAE system and systematic modifications proposed by St Jude researchers has improved its utility for also addressing the long-term effects among childhood cancer survivors.[43] We have aligned our outcome definitions accordingly and by introducing ten additional health conditions of relevance for cancer survivorship research, we wish to further increase the relevance of this classification system.



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The magnitude of late effects is often described with cumulative incidence; however, we encourage the use of the cumulative burden which includes recurrent events as opposed to only first events, thereby reflecting the burden more comprehensively. This is illustrated by a study investigating therapy-related cardiovascular conditions among survivors of childhood and young adult Hodgkin's lymphoma. By the age of 50, cumulative incidence of all grade cardiovascular health conditions did not differ between survivors and controls, while the cumulative burden of the same conditions was almost double in survivors compared to controls.[40] Since none of the measures, however, reflect survivor perspective, we have included the perceived impact of the individual health conditions, psychosocial function and health-related quality of life as reported by the participants. Coupling of objective findings with subjective survivor experiences is essential for interpretation of results and for guiding health-care workers and researchers when choosing which survivorship issues to prioritize.

There are several limitations to our study. A survival time of 3.5 – 14 years at evaluation means that the full spectrum of therapy-related conditions will not be captured. Establishment of the ALL-STAR cohort within the first decade of survival, however, forms the platform for longitudinal follow-up, which is within the overall scope of the project. Interpretation of initial data will be challenged by a heterogenous distribution in both age and survival time, but this will be adjusted for in the statistical analysis. Several of the health conditions evaluated in the ALL-STAR study rely on questionnaire data and subsequent medical chart validation. Low-grade conditions which are not screened for, are therefore likely to be missed. Finally, the ALL-STAR study outcomes are not exhaustive in describing the treatment-related burden. Important outcomes such as semen quality, ovarian reserve, and neurocognitive function were omitted to ensure feasibility of the initial ALL-STAR initiative. Future studies of these important outcomes in the ALL-STAR cohort will benefit from the infrastructure already created.

In conclusion, the ALL-STAR study is establishing a Nordic childhood and young adult ALL survivor cohort to be systematically assessed for the cumulative incidence and burden of treatment-related morbidity. Results will supplement existing knowledge regarding risk of treatment-related morbidity and the underlying possible biological, physical and psychosocial mechanisms, while providing novel insight into differences in survivorship related to specific therapy regimens, health cultures and health care systems. Findings will guide future risk grouping and interventions during treatment and follow-up to ameliorate the burden of therapy without compromising chance of cure.



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**List of abbreviations**

ALL = acute lymphoblastic leukemia; ALL-STAR = Acute Lymphoblastic Leukemia Survivor Toxicity And Rehabilitation; BMD = bone mineral density, BMI = body mass index; BRIEF® = Behavior Rating Inventory of executive Function®; CTCAE = Common Terminology Criteria for Adverse Events; DXA = dual-energy X-ray absorptiometry; ECG = electrocardiogram; FVC = forced vital capacity; GWAS = genome wide association studies; HRV = heart rate variability; MetS = metabolic syndrome; MRI = magnetic resonance imaging; NOPHO = Nordic Society of Pediatric Hematology and Oncology; PROMIS® = Patient Reported Outcomes Measurement Information System®; REDCap® = Research Electronic Data Capture; VO2peak = peak oxygen uptake

**DECLARATIONS**

**Patient consent for publication**

Not applicable

**Availability of data and materials**:

Generated data will be available after completion of the study upon reasonable request.

**Competing interests**

The authors declare that they have no competing interests.

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**Author contributions**

TLF, KS and LAJ devised the study concept, design and protocol. LAJ drafted the manuscript. PHJ and KAM contributed to the cardiac protocol. MKF contributed to the protocol regarding physical performance. AML devised and wrote the protocol regarding oral health. SLM and KGN contributed to the pulmonal protocol. MB contributed to the protocol regarding neuropathy. AH an TLL devised the ultrasound protocols. RBJ, MTS and KMC contributed to the protocol regarding metabolic syndrome and bone density, and MTS to the pancreatic protocol. KG monitored the plan for statistical analyses. LAJ, MTS, KMC, RT, PSW, BKA, KS, TLF contributed to the logistical aspects of the study. All authors contributed to writing and reviewing the manuscript, and made the decision to submit the manuscript for publication

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Figure 1 is created with BioRender.com.

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**Figure 1. ALL-STAR Study overview.**
**Estimated survivors from 475 patients and overall survival rate of 90%.*
***Estimated number of participants based on minimum recruitment rate of 60%.*



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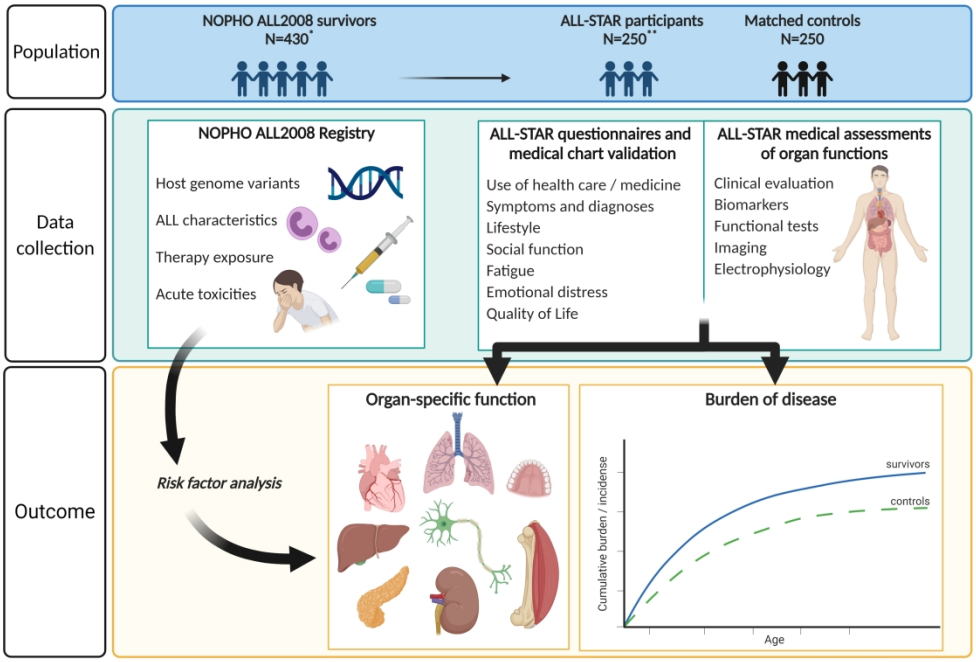


**Figure 1**. ALL-STAR study overview. **Estimated survivors from 475 patients and overall survival rate of 90%. **Estimated number of participants based on minimum recruitment rate of 60%.*

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**Supplementary table 1**. Definitions and grading of 197 health conditions evaluated in the ALL-STAR study according to the St Jude modified version[1] of the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) version 4.03[2]. Health conditions without available definitions from CTCAE v4.03 or the St Jude modified version are inserted with references if readily available and otherwise marked in *italic*.

| **AUDITORY-HEARING** | | | |
|---|---|---|---|
| **Health condition** | **Definition and Grading source** | **Grading** | **ALL-STAR data** |
| Cholesteatoma | Definition:<br>A mass formed by the keratinizing squamous epithelium in the middle ear and/or mastoid, subepithelial connective tissue and by the progressive accumulation of keratin debris with/without surrounding inflammatory reaction.[3]<br><br>Grading source:<br>St Jude modification of CTCAEv4.03<br>Ear and labyrinth disorders:<br>Other, specify | 1: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated<br>2: Moderate; minimal, local or non-invasive intervention indicated; limiting age appropriate instrumental ADL<br>3: Severe or medically significant but not immediately life threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self-care ADL<br>4: Life-threatening consequences; urgent intervention indicated<br>5: Death | - Questionnaire and medical record validation |
| Hearing loss | Definition:<br>A disorder characterized by partial or complete loss of the ability to detect or understand sounds resulting from damage to ear structures. Includes sensorineural, conductive and mixed hearing loss.<br><br>Grading source:<br>St Jude modification of CTCAEv4.03 Ear and labyrinth disorders: Hearing impaired.<br><br>St Jude Modified Chang Ototoxicity Grading Scale:<br><br>Chang KW, Chinosornvatana N. Practical grading system for evaluating cisplatin ototoxicity in children. J Clin Oncol 2010;28(10):1788-95. | 1: ≥ 40 dB at any frequency 6-12 kHz (Chang 1a); > 20 and < 40 dB at 4kHz (Chang 1b)<br>2: ≥ 40 dB at 4 kHz and above (Chang 2a); > 20 and < 40 dB at any frequency <4kHz (Chang 2b)<br>3: ≥ 40 dB at 2 or 3 kHz and above<br>4: ≥ 40 dB at 1 kHz and above<br>5: Not applicable | - Questionnaire and medical record validation |
| Tinnitus | Definition:<br>A disorder characterized by noise in the ears, such as ringing, buzzing, roaring or clicking<br><br>Grading source:<br>CTCAEv4.03<br>Ear and labyrinth disorders:<br>Tinnitus | 1: Mild symptoms; intervention not Indicated<br>2: Moderate symptoms; limiting instrumental ADL<br>3: Severe symptoms; limiting self-care ADL<br>4: Not applicable<br>5: Not applicable | - Questionnaire and medical record validation |

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|---|---|---|---|
| Vertigo | Definition:<br>A disorder characterized by a sensation as if the external world were revolving around the patient (objective vertigo) or as if he himself were revolving in space (subjective vertigo). Includes: Meniere's<br><br>Grading source:<br>CTCAEv4.03<br>Ear and labyrinth disorders:<br>Vertigo | 1: Mild symptoms; intervention not Indicated<br>2: Moderate symptoms; limiting instrumental ADL<br>3: Severe symptoms; limiting self-care ADL<br>4: Not applicable<br>5: Not applicable | - Questionnaire and medical record validation |
| **CARDIOVASCULAR** | | | |
| **Health condition** | **Definition and Grading source** | **Grading** | |
| Aortic root aneurysm | Definition:<br>A permanent localized dilation of the aortic artery having at least a 50% increase in diameter compared to the expected.[4]<br><br>Grading source:<br>St Jude modification of<br>CTCAE v4.03<br>Cardiac Disorders:<br>Other, specify | 1: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated (aortic root >= 3.5 cm to < 4 cm)<br>2: Moderate; minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental ADL (aortic root > = 4 cm)<br>3: Severe or medically significant but not immediately life threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self-care ADL<br>4: Life-threatening consequences; urgent intervention indicated<br>5: Death | - Questionnaire and medical record validation |
| Arteriovenous malformation | Definition:<br>*An abnormal connection between arteries and veins, bypassing the capillary system.*<br><br>Grading source:<br>CTCAE v4.03<br>Cardiac Disorders:<br>Other, specify | 1: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated<br>2: Moderate; minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental ADL<br>3: Severe or medically significant but not immediately life threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self-care ADL<br>4: Life-threatening consequences; urgent intervention indicated<br>5: Death | - Questionnaire and medical record validation |
| Atrioventricular heart block | Definition:<br>Includes: 1st degree (PR> 200msec), 2nd degree, Mobitz I, 2nd degree, Mobitz II, 3rd degree (complete) Bundle branch block, QRS > 120ms, Stokes-Adams Syndrome<br><br>Grading source:<br>CTCAE v4.03<br>Cardiac Disorders:<br>AV Block first degree (grades 1&2); AV block complete; Mobitz (type) II AV block; Mobitz type I (grades 3&4) | 1: Asymptomatic; intervention not indicated<br>2: Symptomatic; non-urgent medical intervention indicated<br>3: Symptomatic and incompletely controlled medically, or controlled with device (e.g., pacemaker)<br>4: Life-threatening consequences; urgent intervention indicated<br>5: Death | - Questionnaire and medical record validation<br>- Electrocardiogram |

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| Bradycardia, sinus | Definition:<br>A disorder characterized by a dysrhythmia with a heart rate less than 50 beats per minute that originates in the sinus node<br><br>Grading source<br>St Jude modification of<br>CTCAE v4.03<br>Cardiac Disorders:<br>Sinus bradycardia | 1: Asymptomatic; intervention not indicated<br>2: Symptomatic; medical intervention indicated<br>3: Severe; medically significant, medical intervention indicated<br>4: Life-threatening consequences; urgent intervention indicated<br>5: Death | - Questionnaire and medical record validation<br>- Electrocardiogram |
| Cardiopulmonary fitness, reduced | Definition:<br>The component of physiologic fitness relating to the ability of the cardiopulmonary system to supply oxygen during sustained physical activity. Reported as number of standard deviations (SD) from the expected mean, based on values from healthy controls.<br><br>Grading source:<br>ALL-STAR research team | 1: Symptomatic; shortness of breath during ADL and moderate physical activity perceived by the patient but not evident on physical exam<br>2: Symptomatic; reduced aerobic performance evident on physical exam; limiting instrumental ADL<br>3: Impaired aerobic performance limiting self-care ADL; < -1.96 SD of age and sex specific healthy control values<br>4: Not applicable<br>5: Not applicable | - Cardiopulmonary fitness test |
| Conduction abnormalities | Definition:<br>Includes: Sick Sinus Syndrome, Wolff-Parkinson-White syndrome<br><br>Grading source:<br>St Jude modification of<br>CTCAE v4.03<br>Cardiac Disorders:<br>Conduction disorder | 1: Asymptomatic or mild symptoms; intervention not indicated<br>2: Moderate symptoms; non-urgent intervention indicated<br>3: Severe symptoms; intervention indicated<br>4: Life-threatening consequences; urgent intervention indicated<br>5: Death | - Questionnaire and medical record validation<br>- Electrocardiogram |
| Congestive heart failure | Definition:<br>A disorder characterized by the inability of the heart to pump blood at an adequate volume to meet tissue metabolic requirements, or, the ability to do so only at an elevation in the filling pressure.<br><br>Grading source:<br>St Jude modification of<br>CTCAE v4.03<br>Cardiac Disorders:<br>Heart failure | 1: Asymptomatic with laboratory (e.g. BNP) or cardiac imaging abnormalities (NYHA I)<br>2: Symptoms with mild to moderate activity or exertion (NYHA II)<br>3: Severe with symptoms at rest or with minimal activity or exertion; intervention indicated (NYHA III)<br>4: Life-threatening consequences; urgent intervention indicated (e.g., continuous IV therapy or mechanical hemodynamic support (NYHA IV)<br>5: Death | - Questionnaire and medical record validation<br>- n-terminal pro brain natriuretic peptide (BNP)<br>- Electrocardiogram<br>- Speckle tracking echocardiography<br>- Cardiac MRI<br>- |

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|---|---|---|---|
| Coronary artery disease | Definition:<br>A disorder characterized by the inability of the heart to pump blood at an adequate volume to meet tissue metabolic requirements, or, the ability to do so only at an elevation in the filling pressure. Includes myocardial infarction.<br><br>Grading source:<br>St Jude modification of<br>CTCAE v4.03<br>Cardiac Disorders:<br>Myocardial infarction | 1: Asymptomatic; clinical or diagnostic observations only; intervention not indicated<br>2: Mild symptoms and cardiac enzymes minimally abnormal and no evidence of ischemic electrocardiogram changes<br>3: Severe symptoms; cardiac enzymes abnormal; hemodynamically stable; electrocardiogram changes consistent with infarction (Q waves)<br>4: Life-threatening consequences; hemodynamically unstable (CABG or angioplasty)<br>5: Death | - Questionnaire and medical record validation<br>- Troponin-T<br>- Electrocardiogram |
| Cor pulmonale (right heart failure) | Definition:<br>A disorder characterized by impairment of right ventricular function associated with low ejection fraction and a decrease in motility of the right ventricular wall<br><br>Grading source<br>CTCAE v4.03<br>Cardiac Disorders:<br>Right ventricular dysfunction | 1: Asymptomatic with laboratory (e.g., BNP) or cardiac imaging abnormalities<br>2: Symptoms with mild to moderate activity or exertion<br>3: Severe symptoms, associated with hypoxia, right heart failure; oxygen indicated<br>4: Life-threatening consequences; urgent intervention indicated (e.g., ventricular assist device); heart transplant indicated<br>5: Death | - Questionnaire and medical record validation<br>- n-terminal pro brain natriuretic peptide<br>- Speckle tracking echocardiography<br>- Cardiac MRI |
| Dysrhythmia | Definition:<br>A disorder characterized by a dysrhythmia originating above the ventricles. Includes: atrial fibrillation, atrial flutter, SVA, SVT, PAT; ventricular arrhythmia, and lethal arrhythmia requiring defibrillation.<br><br>Grading source:<br>CTCAE v4.03<br>Cardiac Disorders:<br>Atrial fibrillation | 1: Asymptomatic, intervention not indicated<br>2: Non-urgent medical intervention indicated<br>3: Symptomatic and incompletely controlled medically, or controlled with device (e.g., pacemaker), or ablation<br>4: Life-threatening consequences; urgent intervention indicated<br>5: Death | - Questionnaire and medical record validation<br>- Electrocardiogram |
| Heart valve disorder | Definition:<br>Disorders characterized by a defect in heart valve function or structure.<br><br>Grading source:<br>St Jude modification of<br>CTCAE v4.03<br>Cardiac Disorders:<br>Aortic valve disease; mitral valve disease; pulmonary valve disease; tricuspid valve disease | 1: Asymptomatic valvular thickening/calcifications with or without mild valvular regurgitation or stenosis by imaging<br>2: Asymptomatic; moderate regurgitation or stenosis by imaging<br>3: Symptomatic; severe regurgitation or stenosis by imaging; symptoms controlled with medical intervention<br>4: Life-threatening consequences; urgent intervention indicated (e.g., valve replacement, valvuloplasty)<br>5: Death | - Questionnaire and medical record validation<br>- Speckle tracking echocardiography<br>- Cardiac MRI |

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| High total cholesterol | Definition:<br>Higher than normal levels of cholesterol in a blood specimen<br><br>Grading source:<br>St Jude modification of CTCAE v4.03<br>Investigations:<br>Cholesterol high<br><br>ALL-STAR modification:<br>Units reported in SI-units, (100mg/dL = 2.59mmol/dL)[5]. | 1: >200 mg/dL - 300 mg/dL (>5.18 mmol/L–7.77 mmol/L)<br>2: >300 - 400 mg/dL (>7.77 mmol/L –10.36 mmol/L); treatment with one lipid lowering agent<br>3: >400 - 500 mg/dL (>10.36 mmol/L –12.95 mmol/L); treatment with >=2 lipid lowering agent<br>4: >500 mg/dL (>12.95 mmol/L)<br>5: Not applicable | | - Questionnaire and medical record validation<br>- Cholesterol level |
| Hypertension (from resting blood pressure) | Definition:<br>A disorder characterized by a pathological increase in blood pressure; a repeatedly elevation in the blood pressure<br><br>Grading source:<br>St Jude modification of CTCAE v4.03<br>Vascular Disorders:<br>Hypertension<br><br>Limits according to National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents.<br>Pediatrics. 2004;114(2 Suppl 4th Report):555. | Adult<br>1: Prehypertension (systolic BP 120 - 139 mm Hg or diastolic BP 80 - 89 mm Hg) | Pediatric<br>1: Prehypertension (systolic and/or diastolic BP >= 90th percentile but < 95th percentile for gender, age and height, or if in adolescents BP exceeds 120/80 mmHg even if <90th percentile) | - Questionnaire and medical record validation<br>- Blood pressure measurement |
| | | 2: Stage 1 hypertension (systolic BP 140 - 159 mm Hg or diastolic BP 90 - 99 mm Hg); medical intervention indicated or initiated; recurrent or persistent (>=24 hrs); symptomatic increase by >20 mm Hg (diastolic) or to >140/90 mm Hg if previously WNL; monotherapy indicated or initiated | 2: Stage 1 hypertension (systolic and/or diastolic BP between the 95th percentile and 5 mmHg above the 99th percentile for gender, age and height, or if in adolescents the BP exceeds 140/90 mmHg even <95th percentile); monotherapy indicated or initiated | |
| | | 3: Stage 2 hypertension (systolic BP >=160 mm Hg or diastolic BP >=100 mm Hg); medical intervention indicated; more than one drug or more intensive therapy than previously used indicated or initiated | 3: Stage 2 hypertension (systolic and/or diastolic BP ≥99th percentile plus 5 mmHg for gender, age, and height); more than one drug or more intensive therapy than previously used indicated or initiated | |
| | | 4: Life-threatening consequences (e.g., malignant hypertension, transient or permanent neurologic deficit, hypertensive crisis); urgent intervention indicated | 4: Life-threatening consequences (e.g., malignant hypertension, transient or permanent neurologic deficit, hypertensive crisis); urgent intervention indicated | |
| | | 5: Death | 5: Death | |

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| Hypertriglyceridemia | Definition:<br>A disorder characterized by laboratory test results that indicate an elevation in the concentration of triglyceride concentration in the blood<br><br>Grading source<br>St Jude modification of<br>CTCAE v4.03<br>Metabolism and Nutrition Disorders:<br>Hypertriglyceridemia<br><br>ALL-STAR modification:<br>Units reported as SI-units, (100mg/dL = 1.13mmol/L)[5] | 1: 150 mg/dL - 300 mg/dL (1.70 mmol/L–3.39 mmol/L)<br>2: >300 mg/dL - 500 mg/dL (>3.39 mmol/L – 5.65 mmol/L); treatment with one lipid lowering agent<br>3: >500 mg/dL - 1000 mg/dL (>5.65 mmol/L – 11.3mmol/L); treatment with >=2 lipid lowering agents<br>4: >1000 mg/dL (>11,3mmol/L); life-threatening consequences<br>5: Death | - Questionnaire and medical record validation<br><br>- Triglyceride level |
| Left ventricular systolic dysfunction | Definition:<br>A disorder characterized by failure of the left ventricle to produce adequate output despite an increase in distending pressure and in end-diastolic volume and reduced ejection fraction. Clinical manifestations may include dyspnea, orthopnea, and other signs and symptoms of pulmonary congestion and edema. Includes cardiomyopathy<br><br>Grading source:<br>St Jude modification of<br>CTCAE v4.03<br>Investigations: Ejection fraction decreased (grades 2&3)<br>Left ventricular systolic dysfunction (grade 4) | 1: Not applicable<br>2: Resting EF < 50-40%; 10 - 19% absolute drop from baseline<br>3: Resting EF 39-20%; >20% absolute drop from baseline; medication indicated or initiated<br>4: Resting EF<20%; refractory or poorly controlled heart failure due to drop in ejection fraction; on medical management; intervention such as ventricular assist device, intravenous vasopressor support, or heart transplant indicated<br>5: Death | - Questionnaire and medical record validation<br>- Speckle tracking echocardiography<br>- Cardiac MRI |
| Pericarditis | Definition:<br>A disorder characterized by irritation to the layers of the pericardium (the protective sac around the heart).<br><br>Grading source:<br>St Jude modification of<br>CTCAE v4.03<br>Cardiac Disorders:<br>Pericarditis | 1: Asymptomatic, electrocardiogram or physical findings (e.g., rub) consistent with pericarditis<br>2: Symptomatic pericarditis (e.g., chest pain)<br>3: Pericarditis with physiologic consequences (e.g., pericardial constriction)<br>4: Life-threatening consequences; urgent intervention indicated (e.g., cardiac tamponade)<br>5: Death | - Questionnaire and medical record validation<br>- Electrocardiogram |

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| Prolonged QTcorrected (QTc) interval | Definition:<br>A finding of a cardiac dysrhythmia characterized by an abnormally long corrected QT interval<br><br>Grading source:<br>St Jude modification of CTCAE v4.03<br>Investigations:<br>Prolonged QTc interval | 1: QTc 460 - 480 ms (men); 470-480 ms (women)<br>2: QTc 481 - 500 ms<br>3: QTc >= 501 ms on >= two separate electrocardiograms<br>4: QTc >= 501 or >60 ms change from baseline and Torsade de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia<br>5: Not applicable | - Questionnaire and medical record validation<br>- Electrocardiogram |
| Pulmonary hypertension | Definition:<br>A disorder characterized by an increase in pressure within the pulmonary circulation due to lung or heart disorder<br><br>Grading source:<br>CTCAE v4.03<br>Respiratory, thoracic, and mediastinal disorders:<br>Pulmonary hypertension | 1: Minimal dyspnea; findings on physical exam or other evaluation<br>2: Moderate dyspnea, cough; requiring evaluation by cardiac catheterization and medical intervention<br>3: Severe symptoms, associated with hypoxemia, right heart failure; oxygen indicated<br>4: Life-threatening airway consequences; urgent intervention indicated (e.g., tracheotomy or intubation)<br>5: Death | - Questionnaire and medical record validation<br>- Speckle tacking echocardiography |
| Raynaud phenomenon | Definition:<br>A clinical disorder consisting of recurrent, long-lasting, and episodic vasospasm of the fingers and toes (rarer in tongue, nose, ears, nipples) often associated with exposure to cold.[6]<br><br>Grading source:<br>St Jude modification of CTCAE v4.03<br>Vascular Disorders:<br>Other, specify | 1: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated<br>2: Moderate; minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental ADL<br>3: Severe or medically significant but not immediately life threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self-care ADL<br>4: Life-threatening consequences; urgent intervention indicated<br>5: Death | - Questionnaire, COMPASS31 and medical record validation |
| Right ventricular systolic dysfunction | Definition:<br>A disorder characterized by impairment of right ventricular function associated with low ejection fraction and a decrease in motility of the right ventricular wall<br><br>Grading source:<br>St Jude modification of CTCAE v4.03<br>Cardiac Disorders:<br>Right ventricular dysfunction | 1: Asymptomatic cardiac imaging abnormalities<br>2: Symptoms with mild to moderate activity or exertion<br>3: Severe symptoms, associated with hypoxia, right heart failure; oxygen indicated<br>4: Life-threatening consequences; urgent intervention indicated (e.g., ventricular assist device); heart transplant indicated<br>5: Death | - Questionnaire and medical record validation<br>- Speckle tacking echocardiography<br>- Cardiac MRI |

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| Tachycardia, sinus | Definition:<br>A disorder characterized by a dysrhythmia with a heart rate greater than 100 beats per minute for adults and greater than 110 beats per minute for children that originates in the sinus node<br><br>Grading source:<br>St Jude modification of CTCAE v4.03<br>Cardiac Disorders:<br>Sinus tachycardia | 1: Asymptomatic, intervention not indicated<br>2: Symptomatic; non-urgent medical intervention indicated<br>3: Urgent medical intervention indicated<br>4: Not applicable<br>5: Not applicable | - Questionnaire and medical record validation<br>- Electrocardiogram |
| Thromboembolic event | Definition:<br>A disorder characterized by occlusion of a vessel by a thrombus that has migrated from a distal site via the blood stream.<br><br>Grading source:<br>St Jude modification of CTCAE v4.03<br>Vascular Disorders: Thromboembolic event | 1: Venous thrombosis (e.g., superficial thrombosis)<br>2: Venous thrombosis (e.g., uncomplicated deep vein thrombosis), medical intervention indicated<br>3: Thrombosis (e.g., non-embolic cardiac mural [arterial] thrombus), medical intervention indicated<br>4: Life-threatening (e.g., cerebrovascular event, arterial insufficiency); hemodynamic or neurologic instability; urgent intervention indicated<br>5: Death | - Questionnaire and medical record validation |
| Vascular disease | Definition:<br>Stenosis/occlusion of vessel other than coronary or cerebral vessels, e.g., carotid, subclavian.<br><br>Grading source:<br>St Jude modification of CTCAE v4.03<br>Vascular Disorders<br>Other, specify | 1: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated<br>2: Moderate; minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental ADL<br>3: Severe or medically significant but not immediately life threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self-care ADL<br>4: Life-threatening consequences; urgent intervention indicated<br>5: Death | - Questionnaire and medical record validation |
| **ENDOCRINE** | | | |
| **Health condition** | **Definition and Grading source** | **Grading** | **Data Grading source** |
| Abnormal glucose metabolism | Definition:<br>A disorder characterized by an inability to properly metabolize glucose. Includes impaired fasting glucose, insulin resistance with impaired glucose tolerance, diabetes mellitus.<br><br>Grading source:<br>St Jude modification of CTCAE v4.03<br>Metabolism and nutrition disorders:<br>Glucose intolerance | 1: Asymptomatic; clinical or diagnostic observations only; pharmacologic intervention not indicated or initiated (e.g. dietary modification)<br>2: Symptomatic; oral agent indicated or initiated<br>3: Severe symptoms; insulin indicated or initiated<br>4: Life threatening consequences, urgent intervention indicated or initiated<br>5: Death | - Questionnaire and medical record validation<br>- Fasting-glucose<br>- HOMA-IR |

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| Adrenal insufficiency | Definition:<br>A disorder that occurs when the adrenal cortex does not produce enough of the hormone cortisol and in some cases, the hormone aldosterone. It may be due to a disorder of the adrenal cortex as in Addison's disease or primary adrenal insufficiency.<br><br>Grading source:<br>St Jude modification of CTCAE v4.03<br>Endocrine disorders:<br>Adrenal insufficiency | 1: Asymptomatic; clinical or diagnostic observations only; intervention indicated during periods of stress<br>2: Moderate symptoms; daily maintenance indicated (i.e. am cortisol < 5 mcg/dL) or initiated<br>3: Severe symptoms; hospitalization indicated<br>4: Life-threatening consequences; urgent intervention indicated<br>5: Death | - Questionnaire and medical record validation |
| Adult growth hormone deficiency | Definition:<br>A finding based on laboratory test results that indicate abnormal levels of growth hormone in a biological specimen<br><br>Grading source:<br>St Jude modification of CTCAE v4.03<br>Investigations:<br>Growth hormone abnormal | 1: Asymptomatic; clinical or diagnostic observations only; intervention not indicated (IGF-1 z-score < -2 in isolation or abnormal dynamic test with decision not to pursue treatment)<br>2: Symptomatic; medical intervention indicated; limiting instrumental ADL<br>3: Not applicable<br>4: Not applicable<br>5: Not applicable | - Questionnaire and medical record validation |
| Childhood growth hormone deficiency | Definition:<br>A finding based on laboratory test results that indicate abnormal levels of growth hormone in a biological specimen<br><br>Grading source:<br>St Jude modification of CTCAE v4.03<br>Investigations:<br>Growth hormone abnormal | 1: Asymptomatic; clinical or diagnostic observations only; intervention not indicated (abnormal dynamic test with decision not to pursue treatment)<br>2: Symptomatic; medical intervention indicated; limiting instrumental ADL<br>3: Not applicable<br>4: Not applicable<br>5: Not applicable | - Questionnaire and medical record validation |
| Diabetes insipidus | Definition:<br>A form of polyuria–polydipsia syndrome characterized by hypotonic polyuria and polydipsia.[7]<br><br>Grading source:<br>St Jude modification of CTCAE v4.03.<br>Endocrine disorders:<br>Other, specify | 1: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated<br>2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL<br>3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self-care ADL<br>4: Life-threatening consequences; urgent intervention indicated<br>5: Death | - Questionnaire and medical record validation |

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| Growth hormone excess | Definition:<br>A finding based on laboratory test results that indicate abnormal levels of growth hormone in a biological specimen<br><br>Grading source:<br>St Jude modification of CTCAE v4.03.<br>Investigations: Growth hormone abnormal | 1: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated<br>2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL<br>3: Death Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self-care ADL<br>4: Life-threatening consequences; urgent intervention indicated<br>5: Death | - Questionnaire and medical record validation |
| Hyperparathyroidism | Definition:<br>A disorder characterized by an increase in production of parathyroid hormone by the parathyroid glands. This results in hypercalcemia (abnormally high levels of calcium in the blood).<br><br>Grading source:<br>St Jude modification of<br>CTCAE v4.03. Endocrine disorders: Hyperparathyroidism | 1: Mild symptoms; intervention not indicated<br>2: Moderate symptoms; medical intervention indicated or initiated<br>3: Not applicable<br>4: Not applicable<br>5: Not applicable | - Questionnaire and medical record validation<br>- Parathyroid hormone<br>- Ionized calcium |
| Hyperprolactinemia | Definition:<br>A disorder of mineral metabolism due to excessive secretion of parathyroid hormone from one or more of the four parathyroid glands.[8]<br><br>Grading source:<br>St Jude modification of<br>CTCAE v4.03. Endocrine disorders: Other, specify | 1: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated<br>2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL<br>3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self-care ADL<br>4: Life-threatening consequences; urgent intervention indicated<br>5: Death | - Questionnaire and medical record validation |
| Hyperthyroidism | Definition:<br>A disorder characterized by excessive levels of thyroid hormone in the body. Common causes include an overactive thyroid gland or thyroid hormone overdose<br><br>Grading source:<br>St Jude modification of<br>CTCAE v4.03<br>Endocrine disorders: Hyperthyroidism | 1: Asymptomatic; clinical or diagnostic observations only; intervention not indicated<br>2: Symptomatic; thyroid suppression indicated or initiated; limiting instrumental ADL<br>3: Severe symptoms; limiting self-care ADL; hospitalization indicated<br>4: Life-threatening consequences; urgent intervention indicated<br>5: Death | - Questionnaire and medical record validation<br>- Thyroid stimulating hormone<br>- Triiodothyronine |

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| Hypoparathyroidism | Definition:<br>A disorder characterized by a decrease in production of parathyroid hormone by the parathyroid glands.<br><br>Grading source:<br>St Jude modification of<br>CTCAE v4.03<br>Endocrine disorders: Hypoparathyroidism | 1: Asymptomatic; clinical or diagnostic observations only; intervention not indicated<br>2: Moderate symptoms; medical intervention indicated or initiated<br>3: Severe symptoms; medical intervention or hospitalization indicated<br>4: Life-threatening consequences; urgent intervention indicated<br>5: Death | | - Questionnaire and medical record validation<br>- Parathyroid hormone<br>- Ionized calcium |
| Hypothyroidism | Definition:<br>A disorder characterized by a decrease in production of thyroid hormone by the thyroid gland. Includes compensated hypothyroidism.<br><br>Grading source:<br>St Jude modification of<br>CTCAE v4.03<br>Endocrine disorders:<br>Hypothyroidism | 1: Asymptomatic; clinical or diagnostic observations only; intervention not indicated (compensated hypothyroidism)<br>2: Symptomatic; thyroid replacement indicated or initiated; limiting instrumental ADL<br>3: Severe symptoms; limiting self- care ADL; hospitalization indicated<br>4: Life-threatening consequences; urgent intervention indicated<br>5: Death | | - Questionnaire and medical record validation<br>- Thyroid stimulating hormone<br>- Triiodothyronine |
| Overweight/Obesity | Definition:<br>A disorder characterized by having a high amount of body fat. Grading source for < 20 years: Criteria per Centers for Disease Control and Prevention guidelines<br><br>Grading source:<br>St Jude modification of<br>CTCAE v4.03<br>Metabolism and nutrition disorders: Obesity<br><br>ALL-STAR modification:<br>Pediatric Grading source according to National, Danish norm material[9]. | For age >= 20 years<br>1: Not applicable<br>2: BMI 25 - 29.9 kg/m2<br>3: BMI 30 - 39.9 kg/m2<br>4: BMI >=40 kg/m2<br>5: Not applicable | For age 2 - <20 years<br>1: Not applicable<br>2: BMI >= 85$^{th}$%ile <95$^{th}$%ile<br>3: BMI $\geq$ 95$^{th}$%ile<br>4: Not applicable<br>5: Not applicable<br><br>ALL-STAR modification:<br>1: Not applicable<br>2: BMI > +1 < +2 standard deviations (84.1%-97.7%)<br>3: BMI > +2 standard deviations (>97.7%)<br>4,5: NA | - Questionnaire and medical record validation<br>- Weight<br>- Height |

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| Sarcopenic obesity | Definition<br>High body fat percentage (BF%) and/or high android fat percentage (AF%) and/or high android/gynoid fat distribution ratio (AG ratio).<br><br>Grading source:<br>ALL-STAR research team<br><br>Standard deviations used for grading are based on results from matched ALL-STAR controls and on the following available sources:<br><br><u>BF% in children:</u><br>Wohlfahrt-Veje et al. Body fat throughout childhood in 2647 healthy Danish children: Agreement of BMI, waist circumference, skinfolds with dual X-ray absorptiometry. Eur J Clin Nutr. 2014;68(6):664–70.<br><br><u>AF% in children:</u><br>Tinggaard J et al. Anthropometry, DXA, and leptin reflect subcutaneous but not visceral abdominal adipose tissue on MRI in 197 healthy adolescents. Pediatr Res. 2017 Oct 1;82(4):620–8.<br><br><u>BF% and AG ratio in adults:</u><br>Miazgowski T et al. Visceral fat reference values derived from healthy European men and women aged 20-30 years using GE Healthcare dual-energy x-ray absorptiometry. PLoS One. 2017 Jul 1;12(7). | 1: Not applicable<br>2: BF% > +1 standard deviations (SD) < +2 SD OR AG > +1 standard deviations (SD) < +2 SD<br>3: BF% > +2 SD OR AG > +2SD<br>4: Not applicable<br>5: Not applicable | 1: Not applicable<br>2: BF% > +1 standard deviations (SD) < +2 SD OR AF% > +1 standard deviations (SD) < +2 SD<br>3: BF% > +2 SD OR AF% > +2SD<br>4: Not applicable<br>5: Not applicable | - DEXA body composition scans |
| Syndrome of inappropriate antidiuretic hormone secretion | Definition:<br>A syndrome characterized by hyponatremia and renal salt loss, unrelated to either renal or adrenal disease, but attributed to overexpansion of body fluids resulting from inappropriate secretion of antidiuretic hormone (ADH).[10]<br><br>Grading source:<br>St Jude modification of CTCAE v4.03<br>Endocrine disorders:<br>Other, specify | 1: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated<br>2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL<br>3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self-care ADL<br>4: Life-threatening consequences; urgent intervention indicated<br>5: Death | | - Questionnaire and medical record validation |

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| Underweight | Definition:<br>Low weight compared to the expected for age and height<br><br>Grading source:<br>St Jude introduced category. Grading source: Criteria per Centers for Disease Control and Prevention guidelines<br><br>ALL-STAR modification:<br>BMI limit expressed as number of standard deviations from the expected mean, based on national Danish reference material[9] | For age >= 20 years<br>1: Not applicable<br>2: BMI < 18.5 kg/m2<br>3: Not applicable<br>4: Not applicable<br>5: Not applicable | For age 2 -< 20 years<br>1: Not applicable<br>2: BMI < 5$^{th}$%ile (< -2SD = <2.3%le)<br>3: Not applicable<br>4: Not applicable<br>5: Not applicable | - Questionnaire and medical record validation<br>- Weight<br>- Height |
| **GASTROINTESTINAL** | | | | |
| **Health condition** | **Definition and Grading source** | **Grading** | | **Data Grading source** |
| Bowel perforation | Definition:<br>A disorder characterized by a rupture in the small intestine wall.<br><br>Grading source:<br>St Jude modification of CTCAEv4.03 Gastrointestinal disorders:<br>Small intestinal perforation | 1: Not applicable<br>2: Symptomatic; medical intervention indicated<br>3: Severe symptoms; elective operative intervention indicated<br>4: Life-threatening consequences; urgent operative intervention indicated<br>5: Death | | - Questionnaire and medical record validation |
| Celiac disease | Definition:<br>An autoimmune disorder occurring in genetically predisposed individuals who develop an immune reaction to gluten.[11]<br><br>Grading source:<br>St Jude modification of CTCAEv4.03 Gastrointestinal disorders:<br>Other, specify | 1: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated<br>2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL<br>3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self-care ADL<br>4: Life-threatening consequences; urgent intervention indicated<br>5: Death | | - Questionnaire and medical record validation |
| Constipation | Definition:<br>A disorder characterized by irregular and infrequent or difficult evacuation of the bowels.<br><br>Grading source:<br>St Jude modification of CTCAEv4.03 Gastrointestinal disorders:<br>Constipation | 1: Not applicable<br>2: Persistent symptoms with regular use of laxatives or enemas; limiting instrumental ADL<br>3: Obstipation with manual evacuation indicated; limiting self-care ADL<br>4: Life-threatening consequences; urgent intervention indicated<br>5: Death | | - Questionnaire, COMPASS31 and medical record validation |

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| Dysphagia | Definition:<br>A disorder characterized by difficulty in swallowing<br><br>Grading source:<br>CTCAEv4.03<br>Gastrointestinal disorders:<br>Dysphagia | 1: Symptomatic, able to eat regular diet<br>2: Symptomatic and altered eating or swallowing<br>3: Severely altered eating or swallowing; tube feeding or TPN or hospitalization indicated<br>4: Life-threatening consequences; urgent intervention indicated<br>5: Death | - Questionnaire and medical record validation |
| Enterocolitis | Definition:<br>A disorder characterized by inflammation of the small and large intestines. Includes: ileitis, typhlitis, colitis, enterocolitis, diverticulitis, Crohn's disease, ulcerative colitis.<br><br>Grading source:<br>St Jude modification of CTCAEv4.03<br>Gastrointestinal disorders:<br>Enterocolitis | 1: Asymptomatic; clinical or diagnostic observations only; intervention not indicated<br>2: Abdominal pain; mucus or blood in stool<br>3: Severe or persistent abdominal pain; fever; ileus; peritoneal signs<br>4 Life-threatening consequences; urgent intervention indicated<br>5: Death | - Questionnaire and medical record validation |
| Esophageal varices | Definition:<br>A disorder characterized by bleeding from esophageal varices<br><br>Grading source:<br>CTCAEv4.03<br>Gastrointestinal disorders:<br>Esophageal varices hemorrhage | 1: Not applicable<br>2: Self-limited; intervention not indicated<br>3: Transfusion, radiologic, endoscopic, or elective operative intervention indicated<br>4: Life-threatening consequences; urgent intervention indicated<br>5: Death | - Questionnaire and medical record validation |
| Esophagitis | Definition:<br>A disorder characterized by inflammation of the esophageal wall.<br><br>Grading source:<br>CTCAEv4.03<br>Gastrointestinal disorders:<br>Esophagitis | 1: Asymptomatic; clinical or diagnostic observations only; intervention not indicated<br>2: Symptomatic; altered eating/swallowing; oral supplements indicated<br>3: Severely altered eating/swallowing; tube feeding, TPN or hospitalization indicated<br>4: Life-threatening consequences; urgent operative intervention indicated<br>5: Death | - Questionnaire and medical record validation |
| Fecal incontinence | Definition:<br>A disorder characterized by inability to control the escape of stool from the rectum.<br><br>Grading source:<br>CTCAEv4.03<br>Gastrointestinal disorders:<br>Fecal incontinence | 1: Occasional use of pads required<br>2: Daily use of pads required<br>3: Severe symptoms; elective operative intervention indicated<br>4: Not applicable<br>5: Not applicable | - Questionnaire, COMPASS31 and medical record validation |

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| Gastritis/duodenitis | Definition:<br>A disorder characterized by inflammation of the stomach<br><br>Grading source:<br>St Jude modification of CTCAEv4.03<br>Gastrointestinal disorders:<br>Gastritis | 1: Asymptomatic; clinical or diagnostic observations only; intervention not indicated<br>2: Symptomatic; altered GI function; medical intervention indicated<br>3: Severely altered eating or gastric function; TPN or hospitalization indicated<br>4: Life-threatening consequences; urgent operative intervention indicated<br>5: Death | - Questionnaire and medical record validation |
| Gastroesophageal reflux disease | Definition:<br>A disorder characterized by reflux of the gastric and/or duodenal contents into the distal esophagus. It is chronic in nature and usually caused by incompetence of the lower esophageal sphincter and may result in injury to the esophageal mucosal. Symptoms include heartburn and acid indigestion.<br><br>Grading source:<br>CTCAEv4.03<br>Gastrointestinal disorders:<br>Gastroesophageal reflux disease | 1: Mild symptoms; intervention not indicated<br>2: Moderate symptoms; medical intervention indicated<br>3: Severe symptoms; surgical intervention indicated<br>4: Not applicable<br>5: Not applicable | - Questionnaire and medical record validation |
| Gastrointestinal fistulas | Definition:<br>A disorder characterized by an abnormal communication between any part of the gastrointestinal system and another organ or anatomic site<br><br>Grading source:<br>CTCAEv4.03<br>Gastrointestinal disorders:<br>Gastrointestinal fistula | 1: Asymptomatic; clinical or diagnostic observations only; intervention not indicated<br>2: Symptomatic; altered GI function<br>3: Severely altered GI function; tube feeding, TPN or hospitalization indicated; elective operative intervention indicated<br>4: Life-threatening consequences; urgent operative intervention indicated<br>5: Death | - Questionnaire and medical record validation |
| Gastrointestinal hemorrhage | Definition:<br>A disorder characterized by bleeding from the upper/lower gastrointestinal tract (oral cavity, pharynx, esophagus, and stomach, small intestine, large intestine, and anus).<br><br>Grading source:<br>St Jude modification of CTCAEv4.03<br>Gastrointestinal disorders:<br>Upper/Lower gastrointestinal hemorrhage | 1: Mild; intervention not indicated<br>2: Moderate symptoms; medical intervention or minor cauterization indicated<br>3: Transfusion; invasive intervention indicated (e.g. radiologic, endoscopic, or elective operative interventions)<br>4: Life-threatening consequences; urgent intervention indicated<br>5: Death | - Questionnaire and medical record validation |

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| Gastrointestinal necrosis | Definition:<br>A disorder characterized by a necrotic process occurring in the gastric/intestinal wall.<br><br>Grading source:<br>St Jude modification of CTCAEv4.03<br>Gastrointestinal disorders:<br>Gastric necrosis | 1: Not applicable<br>2: Not applicable<br>3: Inability to aliment adequately by GI tract; radiologic, endoscopic, or operative intervention indicated<br>4: Life-threatening consequences; urgent operative intervention indicated<br>5: Death | - Questionnaire and medical record validation |
| Gastrointestinal obstruction | Definition:<br>A disorder characterized by blockage of the normal flow of the intestinal contents.<br><br>Grading source:<br>St Jude modification of CTCAEv4.03<br>Gastrointestinal disorders:<br>Small intestinal obstruction | 1: Asymptomatic; clinical or diagnostic observations only; intervention not indicated<br>2: Symptomatic; altered GI function; limiting instrumental ADL<br>3: Hospitalization indicated; elective operative intervention indicated; limiting self -are ADL; disabling<br>4: Life-threatening consequences; urgent operative intervention indicated<br>5: Death | - Questionnaire and medical record validation |
| Gastrointestinal strictures | Definition:<br>A disorder characterized by a narrowing of the lumen of the esophagus/stomach/intestines<br><br>Grading source:<br>St Jude modification of CTCAEv4.03<br>Gastrointestinal disorders:<br>Esophageal stenosis | 1: Asymptomatic; clinical or diagnostic observations only; intervention not indicated<br>2: Symptomatic; altered GI function<br>3: Severely altered GI function; tube feeding; hospitalization indicated; elective operative intervention indicated<br>4: Life-threatening consequences; urgent operative intervention indicated<br>5: Death | - Questionnaire and medical record validation |
| Gastrointestinal ulcer | Definition:<br>A disorder characterized by a circumscribed, inflammatory and necrotic erosive lesion on the mucosal surface of the stomach/intestines<br><br>Grading source:<br>St Jude modification of CTCAEv4.03<br>Gastrointestinal disorders:<br>Gastric ulcer | 1: Asymptomatic; clinical or diagnostic observations only; intervention not indicated<br>2: Symptomatic; altered GI function; medical intervention indicated; limiting instrumental ADLs<br>3: Severely altered GI function; TPN indicated; invasive intervention indicated (e.g. elective operative or endoscopic intervention); limiting self-care ADL; disabling<br>4: Life-threatening consequences; urgent operative intervention indicated<br>5: Death | - Questionnaire and medical record validation |

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| Gastroparesis syndrome | Definition:<br>A chronic disorder characterized by delayed emptying of the stomach after eating, in the absence of any mechanical obstruction.[12]<br><br>Grading source:<br>CTCAEv4.03<br>Gastrointestinal disorders:<br>Gastroparesis | 1: Mild nausea, early satiety and bloating, able to maintain caloric intake on regular diet<br>2: Moderate symptoms; able to maintain nutrition with dietary and lifestyle modifications; may need pharmacologic intervention<br>3: Weight loss; refractory to medical intervention; unable to maintain nutrition orally<br>4: Not applicable<br>5: Not applicable | - Questionnaire, COMPASS31, and medical record validation |
| Malabsorption syndrome | Definition:<br>A disorder characterized by inadequate absorption of nutrients in the small intestine. Symptoms include abdominal marked discomfort, bloating and diarrhea<br><br>Grading source<br>CTCAEv4.03<br>Gastrointestinal disorders:<br>Malabsorption | 1: Not applicable<br>2: Altered diet; oral intervention Indicated<br>3: Inability to aliment adequately; TPN indicated<br>4: Life-threatening consequences; urgent intervention indicated<br>5: Death | - Questionnaire and medical record validation |
| Pancreatic insufficiency | Definition:<br>A finding based on laboratory test results that indicate a decrease in levels of pancreatic enzymes in a biological specimen.<br><br>Grading source:<br>CTCAEv4.03<br>Investigations:<br>Pancreatic enzymes decreased | 1: <LLN and asymptomatic<br>2: Increase in stool frequency, bulk, or odor; steatorrhea<br>3: Sequelae of absorption deficiency<br>4: Not applicable<br>5: Not applicable | - Questionnaire and medical record validation<br>- Fecal elastase |
| Pancreatitis | Definition:<br>A disorder characterized by inflammation of the pancreas<br><br>Grading source:<br>CTCAEv4.03<br>Gastrointestinal disorders:<br>Pancreatitis | 1: Not applicable<br>2: Enzyme elevation or radiologic findings only<br>3: Severe pain; vomiting; medical intervention indicated (e.g., analgesia, nutritional support)<br>4: Life-threatening consequences; urgent intervention indicated<br>5: Death | - Questionnaire and medical record validation<br>- Amylase<br>- Lipase<br>- Ultrasound examination of pancreas |
| Proctitis | Definition:<br>A disorder characterized by inflammation of the rectum.<br><br>Grading source:<br>CTCAEv4.03<br>Gastrointestinal disorders:<br>Proctitis | 1: Rectal discomfort, intervention not indicated<br>2: Symptoms (e.g., rectal discomfort, passing blood or mucus); medical intervention indicated; limiting instrumental ADL<br>3: Severe symptoms; fecal urgency or stool incontinence; limiting self-care ADL<br>4: Life-threatening consequences; urgent intervention indicated<br>5: Death | - Questionnaire and medical record validation |

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| HEPATOBILIARY | | | |
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| **Health condition** | **Definition and Grading source** | **Grading** | **Data Grading source** |
| Cholecystitis/<br>Cholelithiasis | Definition:<br>A disorder characterized by inflammation involving the gallbladder. It may be associated with the presence of gallstones<br><br>Grading source:<br>St Jude modification of CTCAEv4.03<br>Hepatobiliary disorders:<br>Cholecystitis | 1: Not applicable<br>2: Symptomatic; medical intervention indicated<br>3: Severe symptoms; invasive intervention indicated (e.g. radiologic, endoscopic or elective operative intervention)<br>4: Life-threatening consequences; urgent operative intervention indicated<br>5: Death | - Questionnaire and medical record validation |
| Fibrosis/Cirrhosis | Definition:<br>A condition resulting from liver injury leading to necroinflammation and fibrogenesis.[13] Includes patients with Hepatitis B and Hepatitis C induced cirrhosis.<br><br>Grading source:<br>Category and grading according to St Jude<br><br>ALL-STAR modification:<br>ultrasound shear wave elastography (USWE) added | 1: Not applicable<br>2: Not applicable<br>3: Compensated USWE proven or biopsy proven fibrosis/cirrhosis (e.g. asymptomatic thrombocytopenia)<br>4: Decompensated USWE proven or biopsy proven fibrosis/cirrhosis (e.g., coagulopathy, encephalopathy, coma, variceal hemorrhage)<br>5: Death | - Questionnaire and medical record validation<br>- Liver enzymes, INR, albumin, platelets<br>- Hepatic ultrasound including USWE and evaluation of spleen |
| Hepatic failure | Definition:<br>A disorder characterized by the inability of the liver to metabolize chemicals in the body. Laboratory test results reveal abnormal plasma levels of ammonia, bilirubin, lactic dehydrogenase, and alkaline phosphatase.<br><br>Grading source:<br>St Jude modification of CTCAEv4.03<br>Gastrointestinal disorders:<br>Hepatic failure | 1: Not applicable<br>2: Not applicable<br>3: Asterixis; mild encephalopathy; limiting self-care ADL<br>4: Moderate to severe encephalopathy; coma; life threatening consequences; requiring liver transplantation<br>5: Death | - Questionnaire and medical record validation<br>- Liver enzymes, INR, albumin, platelets, bilirubin, LDH |

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| Hepatopathy | Definition:<br>A finding based on laboratory test results that indicate an increase in the level of aspartate aminotransferase (AST or SGOT) and alanine aminotransferase (AST or SGPT) in a blood specimen<br><br>Grading source:<br>CTCAEv4.03<br>Investigations:<br>Alanine and aspartate aminotransferase Increased | 1: >ULN - 3.0 x ULN<br>2: >3.0 - 5.0 x ULN<br>3: >5.0 - 20.0 x ULN<br>4: >20.0 x ULN<br>5: Not applicable | - Questionnaire and medical record validation<br>- Liver enzymes |
| Portal hypertension | Definition:<br>A disorder characterized by an increase in blood pressure in the portal venous system.<br><br>Grading source:<br>CTCAEv4.03<br>Gastrointestinal disorders:<br>Portal hypertension | 1: Not applicable<br>2: Decreased portal vein flow<br>3: Reversal/retrograde portal vein flow; associated with varices and/or ascites<br>4: Life-threatening consequences; urgent intervention indicated<br>5: Death | - Questionnaire and medical record validation<br>- Hepatic ultrasound with Doppler |
| Veno-occlusive disease of liver<br>(Sinusoidal obstructive syndrome) | Definition:<br>A syndrome characterized by at least three of five, otherwise unexplained, criteria: hepatomegaly; hyperbilirubinemia more than UNL; ascites; weight gain of at least 5%; and thrombocytopenia.[14]<br><br>Grading source:<br>St Jude modification of CTCAEv4.03<br>Hepatobiliary disorders:<br>Other, specify | 1: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated<br>2: Moderate; minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental ADL<br>3: Severe or medically significant but not immediately life threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self-care ADL<br>4: Life-threatening consequences; urgent intervention indicated<br>5: Death | - Questionnaire and medical record validation<br>- Weight<br>- Bilirubin, platelets<br>- Abdominal and hepatic ultrasound |

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| HEMATOLOGIC | | | |
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| **Health condition** | **Definition and Grading source** | **Grading** | **Data Grading source** |
| Anemia | Definition:<br>A disorder characterized by a reduction in the amount of hemoglobin in 100 ml of blood. Signs and symptoms of anemia may include pallor of the skin and mucous membranes, shortness of breath, palpitations of the heart, soft systolic murmurs, lethargy, and fatigability.<br><br>Grading source:<br>St Jude modification of CTCAEv4.03<br>Blood and lymphatic disorders: Anemia<br><br>ALL-STAR modification:<br>Units reported as SI-units (100 g/dL = 62 mmol/L) | 1: Hgb <LLN by sex/age-appropriate standards but >=10.0 g/dL (>=6.2 mmol/L)<br>2: Hgb <10.0 - 8.0 g/dL (<6.2 mmol/L–4.96 mmol/L)<br>3: Hgb <8.0 g/dL (< 4.96 mmol/L); transfusion indicated < 4.96 mmol/L<br>4: Life-threatening consequences; urgent intervention indicated<br>5: Death | - Questionnaire and medical record validation<br>- Hemoglobin |
| Coagulopathy | Definition:<br>Includes: disseminated intravascular coagulation, thrombotic thrombocytopenic purpura, hemolytic uremic syndrome, acquired von Willebrand disease, etc.<br><br>Grading source:<br>St Jude modification of CTCAEv4.03<br>Blood and lymphatic disorders: Disseminated intravascular Coagulation | 1: Not applicable<br>2: Not applicable<br>3: Laboratory findings and bleeding<br>4: Life-threatening consequences; urgent intervention indicated<br>5: Death | - Questionnaire and medical record validation<br>- Hematologic blood samples |

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| Iron overload | Definition:<br>Iron overload is defined as excess stores of iron in the body. Excess iron is deposited in organs throughout the body. The most notable organs with iron deposition are the liver, heart, and endocrine glands. Resulting symptoms and disease are related to specific organ damage.[15]<br><br>Grading source:<br>Category and grading according to St Jude<br><br>ALL-STAR modification:<br>Ferritin limit of 1000 ng/mL added to grade 2 since this value is often used as indicative of therapy in hematologic patients.[16] | 1: Tissue iron overload confirmed by imaging (e.g., T2*) or biopsy; intervention not indicated<br>2: Tissue iron overload confirmed by imaging (e.g., T2*) or biopsy; phlebotomy or oral chelation therapy indicated or initiated or ferritin > 1000 ng/mL<br>3: Tissue iron overload confirmed by imaging (e.g., T2*) or biopsy; intravenous or subcutaneous chelation therapy indicated or initiated<br>4: Life-threatening consequences; urgent intervention indicated or initiated; liver transplantation indicated or completed<br>5: Death | - Questionnaire and medical record validation<br>- Ferritin<br>- Cardiac MRI T2* |
| Neutropenia | Definition:<br>A finding based on laboratory test results that indicate a decrease in number of neutrophils in a blood specimen.<br><br>Grading source:<br>St Jude modification of CTCAEv4.03<br>Investigations:<br>Neutrophil count decreased<br><br>ALL-STAR modification:<br>Units reported as SI units. (1000 unit/mm3 = $1x10^{-9}$/L) | 1: <1500 - 1000/mm3 (<$1.5*10^{-9}$/L –$1*10^{-9}$/L)<br>2: <1000 - 500/mm3 (<$1*10^{-9}$/L –$0.5*10^{-9}$/L)<br>3: <500/mm3 (<$0.5*10^{-9}$/L)<br>4: Not applicable<br>5. Not applicable | - Questionnaire and medical record validation<br>- Neutrophil count |
| Polycythemia | Definition:<br>A finding based on laboratory test results that indicate increased levels of hemoglobin in a biological specimen<br><br>Grading source:<br>St Jude modification of CTCAEv4.03<br>Investigations:<br>Hemoglobin increased<br><br>ALL-STAR modification:<br>Units reported as SI units. (100 g/dL = 62mmol/L) | 1: Increase in >0 - 2 g/dL (>0–1.24 mmol/L) ULN or above baseline if baseline is above ULN<br>2: Increase in >2 - 4 g/dL (>1.24–2.48 mmol/L) above ULN or above baseline if baseline is above ULN; requiring phlebotomy or other medical intervention.<br>3: Increase in >4 g/dL (>2.48 mmol/L) above ULN or above baseline if baseline is above ULN<br>4: Not applicable<br>5. Not applicable | - Questionnaire and medical record validation<br>- Hemoglobin |

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| Thrombocytopenia | Definition:<br>Definition: A finding based on laboratory test results that indicate a decrease in number of platelets in a blood specimen.<br><br>Grading source:<br>CTCAEv4.03<br>Investigations:<br>Platelet count decreased<br><br>ALL-STAR modification:<br>Units reported as SI units. (1000 unit/mm3 = $1x10^{-9}$/L) | 1: Platelets <LLN - 75,000/mm3 ($75*10^{-9}$/L)<br>2: <75,000 - 50,000/mm3 ($<75–50*10^{-9}$/L)<br>3: <50,000 - 25,000/mm3 ($<50–25*10^{-9}$/L)<br>4: <25,000/mm3 ($<25*10^{-9}$/L)<br>5: Not applicable | - Questionnaire and medical record validation<br>- Platelet count |
| Thrombocytosis | Definition:<br>*Elevated number of platelets in the blood.*<br><br>Grading source:<br>St Jude modification of CTCAEv4.03<br>Blood and lymphatic disorders:<br>Other, specify | 1: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated<br>2: Moderate; minimal, local or non-invasive intervention indicated; limiting age appropriate instrumental ADL<br>**3:** Severe or medically significant but not immediately life threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self-care ADL<br>4: Life-threatening consequences; urgent intervention indicated<br>5: Death | - Questionnaire and medical record validation<br>- Platelet count |
| **IMMUNOLOGIC** | | | |
| **Health condition** | **Definition and Grading source** | **Grading** | **Data Grading source** |
| Autoimmune disorders | Definition:<br>A disorder resulting from loss of function or tissue destruction of an organ or multiple organs, arising from humoral or cellular immune responses of the individual to his own tissue constituents. (Includes: sarcoidosis, collagen vascular diseases -- rheumatoid arthritis, systemic lupus erythematosus, scleroderma, dermatomyositis, polyarteritis nodosa)<br><br>Grading source:<br>St Jude modification of CTCAEv4.03<br>Immune system disorders:<br>Autoimmune disorder | 1: Asymptomatic; serologic or other evidence of autoimmune reaction, with normal organ function; intervention not indicated<br>2: Evidence of autoimmune reaction involving a nonessential organ or function (e.g., hypothyroidism)<br>3: Autoimmune reactions involving major organ (e.g., colitis, anemia, myocarditis, kidney)<br>4: Life-threatening consequences; urgent intervention indicated<br>5: Death | - Questionnaire and medical record validation |

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| Graft-versus-host disease | Definition:<br>A complication of allogeneic hematopoietic stem cell transplantation involving inflammation, cell-mediated immunity, humoral immunity, and fibrosis and resulting in a syndrome of variable clinical features resembling autoimmune and other immunologic disorders.[17]<br><br>Grading source:<br>St Jude modification of CTCAEv4.03<br>Immune system disorders:<br>Other, specify | 1: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated or initiated<br>2: Moderate; minimal, local or non-invasive intervention indicated or initiated; limiting age appropriate instrumental ADL<br>3: Severe or medically significant but not immediately life threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self-care ADL<br>4: Life-threatening consequences; urgent intervention indicated<br>5: Death | - Questionnaire and medical record validation |
| Immunodeficiency | Definition:<br>Includes: hypogammaglobulinemia IgA deficiency, immunodeficiency NOT due to HIV or other infectious/neoplastic processes<br><br>Grading source:<br>St Jude modification of CTCAEv4.03<br>Immune system disorders:<br>Other, specify | 1: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated or initiated<br>2: Moderate; minimal, local or non-invasive intervention indicated (e.g. IVIG) or initiated; limiting age appropriate instrumental ADL<br>3: Severe or medically significant but not immediately life threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self-care ADL<br>4: Life-threatening consequences; urgent intervention indicated<br>5: Death | - Questionnaire and medical record validation<br>- Immunoglobulin levels |
| **INFECTIONS** | | | |
| **Health condition** | **Definition and Grading source** | **Grading** | |
| Bronchial/lung infections. Chronic and/or recurrent | Definition:<br>A disorder characterized by an infectious process involving the lungs. Defined as 3 infections in 6 months.<br><br>Grading source:<br>St Jude modification of CTCAEv4.03<br>Infections and infestations:<br>Lung infection | 1: Not applicable<br>2: Moderate symptoms; oral intervention indicated or initiated (e.g., antibiotic, antifungal, antiviral)<br>3: IV antibiotic, antifungal, or antiviral intervention indicated or initiated; invasive intervention indicated (e.g., radiologic, endoscopic, or operative intervention)<br>4: Life-threatening consequences; urgent intervention indicated<br>5: Death | - Questionnaire and medical record validation |
| Endocarditis infective | Definition:<br>A disorder characterized by an infectious process involving the endocardial layer of the heart.<br><br>Grading source:<br>St Jude modification of CTCAEv4.03<br>Infections and infestations:<br>Endocarditis infective | 1: Not applicable<br>2: Not applicable<br>3: IV antibiotic, antifungal, or antiviral intervention indicated or initiated; invasive intervention indicated (e.g., radiologic or operative intervention)<br>3: Life-threatening consequences; urgent intervention indicated<br>4: Death | - Questionnaire and medical record validation |

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| Gastrointestinal infection | Definition:<br>A disorder characterized by an infectious process involving the gastrointestinal tract. Includes: appendicitis diverticulitis, typhlitis, esophagitis, gastritis, and enterocolitis.<br><br>Grading source:<br>St Jude modification of CTCAEv4.03<br>Infections and infestations:<br>Small intestine infection | 1: Not applicable<br>2: Moderate symptoms; oral intervention indicated or initiated (e.g., antibiotic, antifungal, antiviral)<br>3: IV antibiotic, antifungal, or antiviral intervention indicated or initiated; invasive intervention indicated (e.g., radiologic, endoscopic, or operative intervention)<br>4: Life-threatening consequences; urgent intervention indicated<br>5: Death | - Questionnaire and medical record validation |
| Genitourinary infection | Definition:<br>A disorder characterized by an infectious process involving the urinary tract, most commonly the bladder and the urethra<br><br>Grading source:<br>St Jude modification of CTCAEv4.03<br>Infections and infestations:<br>Urinary tract infection | 1: Not applicable<br>2: Oral intervention indicated or initiated (e.g., oral or topical antibiotic, antifungal, antiviral)<br>3: IV antibiotic, antifungal, or antiviral intervention indicated or initiated; invasive intervention indicated (e.g., radiologic, endoscopic, or operative intervention)<br>4: Life-threatening consequences; urgent intervention indicated<br>5: Death | - Questionnaire and medical record validation<br>- Urine leucocytes and nitrite |
| Hepatitis B, chronic | Definition:<br>A disorder characterized by a viral pathologic process involving the liver parenchyma.<br><br>Grading source:<br>St Jude modification of CTCAEv4.03<br>Infections and infestations:<br>Hepatitis viral | 1: Asymptomatic<br>2: Asymptomatic but treated with antiviral therapy<br>3: Symptomatic liver dysfunction; fibrosis by biopsy; compensated cirrhosis; hospitalization or prolongation of existing hospitalization indicated<br>4: Decompensated liver function (e.g., coagulopathy, encephalopathy, coma, variceal hemorrhage)<br>5: Death | - Questionnaire and medical record validation<br>- HBV antibodies |
| Hepatitis C, chronic | Definition:<br>A disorder characterized by a viral pathologic process involving the liver parenchyma.<br><br>Grading source:<br>St Jude modification of CTCAEv4.03<br>Infections and infestations:<br>Hepatitis viral | 1: Asymptomatic<br>2: Asymptomatic but treated with antiviral therapy<br>3: Symptomatic liver dysfunction; fibrosis by biopsy; compensated cirrhosis; hospitalization or prolongation of existing hospitalization indicated<br>4: Decompensated liver function (e.g., coagulopathy, encephalopathy, coma, variceal hemorrhage)<br>5: Death | - Questionnaire and medical record validation<br>- HCV antibodies |

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| HIV infection | Definition:<br>*Infection with human immunodeficiency virus.*<br><br>Grading source:<br>St Jude modification of CTCAEv4.03<br>Infections and infestations:<br>Other, specify | 1: Asymptomatic or mild symptoms; clinical or diagnostic observations only<br>2: Moderate; minimal, local or noninvasive intervention indicated or initiated (e.g., HAART therapy); limiting age appropriate instrumental ADL<br>3: Severe or medically significant but not immediately life threatening, including sequelae of opportunistic infection; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self-care ADL<br>4: Life-threatening consequences; urgent intervention indicated<br>5: Death | - Questionnaire and medical record validation |
| Lymphatic infection | Definition:<br>A disorder characterized by an infectious process involving the lymph nodes<br><br>Grading source<br>St Jude modification of CTCAEv4.03<br>Infections and infestations:<br>Lymph gland infection | 1: Not applicable<br>2: Localized; local intervention indicated or initiated (e.g., topical antibiotic, antifungal, or antiviral)<br>3: IV antibiotic, antifungal, or antiviral intervention indicated or initiated; invasive intervention indicated (e.g., radiologic or operative intervention)<br>4: Life-threatening consequences; urgent intervention indicated<br>5: Death | - Questionnaire and medical record validation |
| Meningoencephalitis | Definition:<br>A disorder characterized by acute inflammation of the meninges of the brain and/or spinal cord.<br><br>Grading source:<br>St Jude modification of CTCAEv4.03<br>Infections and infestations:<br>Meningitis | 1: Not applicable<br>2: Not applicable<br>3: IV antibiotic, antifungal, or antiviral intervention indicated or initiated; invasive intervention indicated (e.g., radiologic or operative intervention); focal neurologic deficit<br>4: Life-threatening consequences; urgent intervention indicated<br>5: Death | - Questionnaire and medical record validation |
| Osteomyelitis | Definition:<br>A disorder characterized by an infectious process involving the bones.<br><br>Grading source:<br>St Jude modification of CTCAEv4.03<br>Infections and infestations:<br>Bone infection | 1: Not applicable<br>2: Not applicable<br>3: IV antibiotic, antifungal, or antiviral intervention indicated or initiated; invasive intervention indicated (e.g., radiologic or operative intervention)<br>4: Life-threatening consequences; urgent intervention indicated<br>5: Death | - Questionnaire and medical record validation |

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| Otitis media, chronic/recurrent | Definition:<br>A disorder characterized by an infectious process involving the middle ear. Defined as 3 infections in 6 months.<br><br>Grading source:<br>St Jude modification of CTCAEv4.03<br>Infections and infestations:<br>Otitis media | 1: Not applicable<br>2: Localized; local intervention indicated or initiated (e.g., topical antibiotic, antifungal, or antiviral)<br>3: IV antibiotic, antifungal, or antiviral intervention indicated or initiated; invasive intervention indicated (e.g., radiologic or operative intervention)<br>4: Life-threatening consequences; urgent intervention indicated<br>5: Death | - Questionnaire and medical record validation |
| Pelvic inflammatory disease | Definition:<br>A disorder characterized by an infectious process involving the pelvic cavity<br><br>Grading source:<br>St Jude modification of CTCAEv4.03<br>Infections and infestations:<br>Pelvic infection | 1: Not applicable<br>2: Moderate symptoms; oral intervention indicated or initiated (e.g., antibiotic, antifungal, antiviral)<br>3: IV antibiotic, antifungal, or antiviral intervention indicated or initiated; invasive intervention indicated (e.g., radiologic or operative intervention)<br>4: Life-threatening consequences; urgent intervention indicated<br>5: Death | - Questionnaire and medical record validation |
| Pharyngitis/tonsillitis, chronic/recurrent | Definition: A disorder characterized by inflammation of the throat. Defined as 3 infections in 6 months<br><br>Grading source:<br>St Jude modification of CTCAEv4.03<br>Infections and infestations:<br>Pharyngitis<br><br>ALL-STAR modification:<br>Includes also tonsillectomy due to recurring infections | 1: Not applicable<br>2: Localized; local intervention indicated or initiated (e.g., topical antibiotic, antifungal, or antiviral)<br>3: IV antibiotic, antifungal, or antiviral intervention indicated or initiated; invasive intervention indicated (e.g., radiologic, endoscopic, or operative intervention)<br>4: Life-threatening consequences; urgent intervention indicated<br>5: Death | - Questionnaire and medical record validation |
| Sinusitis, chronic/recurrent | Definition:<br>A disorder characterized by an infectious process involving the mucous membranes of the paranasal sinuses. Defined as 3 infections in 6 months.<br><br>Grading source:<br>St Jude modification of CTCAEv4.03<br>Infections and infestations:<br>Sinusitis<br><br>ALL-STAR modification:<br>Chronic is defined as lasting more than 12 weeks | 1: Not applicable<br>2: Localized; local intervention indicated or initiated (e.g., topical antibiotic, antifungal, or antiviral)<br>3: IV antibiotic, antifungal, or antiviral intervention indicated or initiated; invasive intervention indicated (e.g., radiologic, endoscopic, or operative intervention)<br>4: Life-threatening consequences; urgent intervention indicated<br>5: Death | - Questionnaire and medical record validation |

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| Soft tissue infection | Definition:<br>A disorder characterized by an infectious process involving soft tissues.<br><br>Grading source:<br>St Jude modification of CTCAEv4.03<br>Infections and infestations:<br>Soft tissue infection | 1: Not applicable<br>2: Moderate symptoms; oral intervention indicated or initiated (e.g., antibiotic, antifungal, antiviral)<br>3: IV antibiotic, antifungal, or antiviral intervention indicated or initiated; invasive intervention indicated (e.g., radiologic or operative intervention)<br>4: Life-threatening consequences; urgent intervention indicated<br>5: Death | - Questionnaire and medical record validation |
| **MUSCULOSKELETAL** | | | |
| **Health condition** | **Definition and Grading source** | **Grading** | **ALL-STAR data** |
| Amputation | Definition:<br>*Removal of a limb.*<br><br>Grading source:<br>Category and grading according to St Jude and<br><br>ICD-9-CM Diagnosis and Procedure Codes: Abbreviated and Full Code Titles. Centers for Medicare & Medicaid Services <https://www.cms.gov/medicare/coding/ICD9providerdiagnosticcodes/codes.html#><br><br>ALL-STAR modification: IDC-10 Version 2019. https://icd.who.int/browse10/2019/en> | 1: Partial ostectomy or other bone repair<br>2: Amputation below ankle or below elbow; revision of amputation<br>3: Total ostectomy; upper extremity amputation above elbow or higher; lower extremity amputation above ankle or higher<br>4: Not applicable<br>5: Not applicable | - Questionnaire and medical record validation |
| Arthralgia | Definition:<br>A disorder characterized by a sensation of marked discomfort in a joint<br><br>Grading source:<br>CTCAEv4.03<br>Musculoskeletal & connective tissue disorders:<br>Arthralgia | 1: Mild pain<br>2: Moderate pain; limiting instrumental ADL<br>3: Severe pain; limiting self-care ADL<br>4: Not applicable<br>5: Not applicable | - Questionnaire and medical record validation |
| Arthritis | Definition:<br>A disorder characterized by inflammation involving a joint.<br><br>Grading source:<br>CTCAEv4.03<br>Musculoskeletal & connective tissue disorders:<br>Arthritis | 1: Mild pain with inflammation, erythema, or joint swelling<br>2: Moderate pain associated with signs of inflammation, erythema, or joint swelling; limiting instrumental ADL<br>3: Severe pain associated with signs of inflammation, erythema, or joint swelling; irreversible joint damage; disabling; limiting self-care ADL<br>4: Not applicable<br>5: Not applicable | - Questionnaire and medical record validation |

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| Bone mineral density deficit | Definition:<br>A disorder characterized by reduced bone mass, with a decrease in cortical thickness and in the number and size of the trabeculae of cancellous bone (but normal chemical composition), resulting in increased fracture incidence.<br><br>Grading source<br>St Jude modification of CTCAEv4.03<br>Musculoskeletal & connective tissue disorders:<br>Osteoporosis<br><br>-and-<br><br>New Grading source (Pediatric)<br>International Society of Clinical Densitometry | Adults<br>1: Radiologic evidence of osteoporosis or Bone Mineral Density (BMD) t-score -1 to -2.5 (osteopenia); no loss of height or intervention indicated;<br>2: BMD t-score <-2.5; loss of height <2 cm; anti-osteoporotic therapy indicated or initiated; therapy to improve BMD indicated or initiated; limiting instrumental ADL;<br>3: Loss of height >=2 cm; hospitalization indicated; limiting self-care ADL<br>4: Not applicable<br>5: Not applicable | Pediatric<br>1: Radiologic evidence of low BMD with z score of ≤-2.0 and no history of significant fractures<br>2: Low BMD (z-score ≤-2.0) and significant fracture history (defined as a long bone fracture of the lower extremity, vertebral compression, 2 or more long bone fracture of the upper extremities); therapy to improve BMD indicated or initiated<br>3: Limiting self-care ADL<br>4: Not applicable<br>5: Not applicable | - Questionnaire and medical record validation<br>- DXA bone scan |
| Hernia | Definition:<br>Includes: abdominal, umbilical, ventral, inguinal, femoral, etc.<br><br>Grading source:<br>St Jude modification of CTCAEv4.03<br>Musculoskeletal & connective tissue disorders:<br>Other, specify | 1: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated<br>2: Moderate; minimal, local or non-invasive intervention indicated; limiting age appropriate instrumental ADL<br>3: Severe or medically significant but not immediately life threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self-care ADL<br>4: Life-threatening consequences; urgent intervention indicated<br>5: Death | | - Questionnaire and medical record validation |
| Intervertebral disc disorder | Definition:<br>Includes: disc degeneration, disc herniation<br><br>Grading source:<br>St Jude modification of CTCAEv4.03<br>Musculoskeletal & connective tissue disorders:<br>Other, specify | 1: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated<br>2: Moderate; minimal, local or non-invasive intervention indicated; limiting age appropriate instrumental ADL<br>3: Severe or medically significant but not immediately life threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self -care ADL<br>4: Life-threatening consequences; urgent intervention indicated<br>5: Death | | - Questionnaire and medical record validation |

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| Kyphosis | Definition:<br>A disorder characterized by an abnormal increase in the curvature of the thoracic portion of the spine.<br><br>Grading source<br>St Jude modification of CTCAEv4.03<br>Musculoskeletal & connective tissue disorders:<br>Kyphosis | 1: Not applicable<br>2: Moderate accentuation; limiting instrumental ADL<br>3: Severe accentuation; operative intervention indicated; limiting self-care ADL<br>4: Not applicable<br>5: Not applicable | - Questionnaire and medical record validation |
| Limb length discrepancy | Definition:<br>A disorder characterized by of a discrepancy between the lengths of the lower or upper extremities<br><br>Grading source:<br>St Jude modification of CTCAEv4.03<br>Musculoskeletal & connective tissue disorders:<br>Unequal limb length | 1: Not applicable<br>2: Moderate length discrepancy 2-5 cm; shoe lift indicated; limiting instrumental ADL<br>3: Severe length discrepancy >5 cm; limiting self-care ADL; disabling; operative intervention indicated<br>4: Not applicable<br>5: Not applicable | - Questionnaire and medical record validation |
| Osteonecrosis | Definition:<br>A disorder characterized by necrotic changes in the bone tissue due to interruption of blood supply. Most often affecting the epiphysis of the long bones, the necrotic changes result in the collapse and the destruction of the bone structure.<br><br>Grading source:<br>St Jude modification of CTCAEv4.03<br>Musculoskeletal & connective tissue disorders:<br>Avascular necrosis | 1: Asymptomatic; clinical or diagnostic observations only; intervention not indicated<br>2: Symptomatic; medical intervention indicated (e.g., analgesics, anti-inflammatory); limiting instrumental ADL<br>3: Severe symptoms; limiting self-care ADL; elective operative intervention indicated<br>4: Life-threatening consequences; urgent intervention indicated<br>5: Death | - Questionnaire and medical record validation |
| Palatal defects, acquired | Definition:<br>*Palatal defect not present at birth*<br><br>Grading source:<br>St Jude modification of CTCAEv4.03<br>Musculoskeletal & connective tissue disorders:<br>Other, specify | 1: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated<br>2: Moderate; minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental ADL<br>3: Severe or medically significant but not immediately life threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self-care ADL<br>4: Life-threatening consequences; urgent intervention indicated<br>5: Death | - Questionnaire and medical record validation |

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| Scoliosis | Definition:<br>A disorder characterized by a malformed, lateral curvature of the spine.<br><br>Grading source:<br>St Jude modification of CTCAEv4.03<br>Musculoskeletal & connective tissue disorders:<br>Scoliosis | 1: > 8 and <15 degrees; clinically undetectable<br>2: >=15 - 30 degrees; visible by forward flexion; limiting instrumental ADL<br>3: >=30 degrees; scapular prominence in forward flexion; operative intervention indicated; limiting self-care ADL; disabling<br>4: Not applicable<br>5: Not applicable | - Questionnaire and medical record validation |
| Skeletal spine disorder | Definition:<br>Includes: spondylitis, spondylolisthesis, spondylomalacia, spondydylosis<br><br>Grading source:<br>St Jude modification of CTCAEv4.03<br>Musculoskeletal & connective tissue disorders:<br>Other, specify | 1: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated<br>2: Moderate; minimal, local or non-invasive intervention indicated; limiting age appropriate instrumental ADL<br>3: Severe or medically significant but not immediately life threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self-care ADL<br>4: Life-threatening consequences; urgent intervention indicated<br>5: Death | - Questionnaire and medical record validation |
| Slipped capital femoral epiphysis | Definition:<br>Posterior and inferior displacement of the femoral epiphysis relative to the femoral head and neck.[18]<br><br>Grading source:<br>St Jude modification of CTCAEv4.03<br>Musculoskeletal & connective tissue disorders:<br>Other, specify | 1: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated<br>2: Moderate; minimal, local or non-invasive intervention indicated; limiting age appropriate instrumental ADL<br>3: Severe or medically significant but not immediately life threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self-care ADL<br>4: Life-threatening consequences; urgent intervention indicated<br>5: Death | - Questionnaire and medical record validation |
| **ORAL-DENTAL** | | | |
| **Health condition** | **Definition and Grading source** | **Grading** | **ALL-STAR data** |
| Dental caries | Definition:<br>A biofilm-mediated, sugar-driven, multifactorial disease that results in the phasic demineralization and remineralization of dental hard tissues.[19]<br><br>Grading source:<br>ALL-STAR research team.<br>Decayed Missed Filled (DMF)-teeth/surfaces scoring system and International Caries Detection and Assessment System (ICDAS).[19] | 1: No clinical visible carious lesions.<br>2: Initial caries, non-cavitated (may be white, yellow/brown); dental intervention needed including preventive measures.<br>3: Carious lesion in enamel with cavity; dental restoration needed.<br>4: Shadow from dentin with or without localized enamel breakdown; dental treatment needed.<br>5: Distinct and extensive distinct cavity with visible dentine; dental restoration, and/or endodontic treatment, or extraction; disabling. | - Questionnaire and medical record validation<br>- Dental evaluation |

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| Dental erosion | Definition:<br>A condition characterized by loss or wear of dental hard tissue by acids and not caused by bacteria.<br>May be caused by intrinsic (e.g., acid reflux and excessive vomiting) and/or extrinsic (e.g., diet) factors.[20]<br><br>Grading source:<br>ALL-STAR research team.<br>Basic Erosive Wear Examination (BEWE)-score.[21] | 1: No surface loss<br>2: Initial loss of enamel surface texture<br>3: Distinct defect, hard tissue loss (dentine) less than 50% of the surface area<br>4: Hard tissue loss more than 50% of the surface area. Disabling.<br>5: Not applicable. | - Questionnaire and medical record validation<br>- Dental evaluation |
| Gingivitis | Definition:<br>Inflammation of the gums includes gingival redness, edema, bleeding on slight provocation or spontaneously, and swelling with loss of stippling. Difficulty in chewing. Gingivitis can lead to periodontitis.[22–24]<br><br>Grading source:<br>ALL-STAR research team.<br>Plaque index and gingival index.[22,23] | 1: No plaque, No inflammation<br>2: A film of plaque adhering to the free gingival margin and adjacent area of the tooth. Mild inflammation.<br>3: Moderate accumulation of soft deposits within the gingival pocket, or the tooth and gingival margin, which can be seen with the naked eye. Moderate inflammation with bleeding on probing.<br>4: Abundance of soft matter within the gingival pocket and/or on the tooth and gingival margin.Severe inflammation and tendency to spontaneous bleeding. Dental intervention needed.<br>5: Not applicable. | - Questionnaire and medical record validation<br>- Dental evaluation |
| Periodontitis | Definition:<br>A chronic multifactorial inflammatory disease associated with dysbiotic plaque biofilms and characterized by progressive destruction of the tooth-supporting apparatus. Its primary features include the loss of periodontal tissue support, manifested through clinical attachment loss (CAL) and radiographically assessed alveolar bone loss, presence of periodontal pocketing and gingival bleeding.[25]<br><br>Grading source:<br>ALL-STAR research team.<br>Plaque index, gingival index, periodontal pocket depth assessment.[22,23,25] | 1: Mild to moderate periodontitis<br>2: Moderate to severe periodontitis<br>Based on bleeding on<br>probing scores and probing pocket depths > 5 mm etc.<br>3: Tooth loss due to periodontitis<br>4: All stages require dental intervention, from preventive measure to oral rehabilitation.<br>5: Not applicable. | - Questionnaire and medical record validation<br>- Dental/periodontal evaluation |

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| Acute sialadenitis | Definition:<br>Acute inflammation of salivary glands, usually the major ones, and most commonly the parotid gland, followed by submandibular and sublingual glands. May be induced by infection, medication autoimmune or metabolic disease.[26]<br><br>Grading source:<br>ALL-STAR research team | 1: Not applicable<br>2: Painful swelling<br>reddened skin, edema of the cheek and neck; medical intervention indicated.<br>3: Low-grade fever, malaise, elevated ESR, CRP, leukocytosis, purulent exudate from duct orifice; urgent intervention indicated.<br>4: Life-threatening consequences; urgent intervention indicated.<br>5: Not applicable | - Questionnaire and medical record validation<br>- Orofacial evaluation including inspection and palpation, sialometry |
| Chronic sialadenitis | Definition<br>Chronic inflammation of salivary glands, usually the major ones, and most commonly the parotid gland, followed by submandibular and sublingual glands. May be induced by infection, medication autoimmune or metabolic disease.[26]<br><br>Grading source:<br>ALL-STAR research team | 1: Mild pain and swelling.<br>2: Moderate pain and swelling/recurrent swellings, related to meals, often unilateral<br>3: reddened duct orifice and decreased salivary flow.<br>4: Severe pain and secondary infection; medical intervention indicated.<br>5: Not applicable. | - Questionnaire and medical record validation<br>- Orofacial evaluation including inspection and palpation, sialometry |
| Salivary gland dysfunction | Definition:<br>A condition characterized by changes in salivary flow, amount, and/or quality of saliva produced. Most commonly hyposalivation and xerostomia.[27]<br><br>Grading source:<br>ALL-STAR research team.<br>Measurement of whole saliva flow rates (sialometry); Xerostomia Inventory (XI); Visual Analogue Scale; Clinical Oral Dryness Score (CODS).[28] | 1: Mild symptoms of xerostomia; normal unstimulated (UWS, 0.3-0.5 ml/min) and chewing-stimulated whole saliva (SWS, 1-3 ml/min) flow rates.<br>2: Mild-moderate symptoms and low secretors (UWS 0.2 ml/min).<br>3: Severe symptoms and hyposalivation (UWS ≤ 0.1 ml/min, and SWS ≤ 0.70 ml/min).<br>4: Persistent hyposalivation with clinical consequences including dental caries, dental erosion, gingivitis, mucosal ulcerations and infections, difficulties chewing, swallowing, taste and speech etc.; dental and medical intervention; impact on food intake; disabling.<br>5: Not applicable. | - Questionnaire and medical record validation<br>- Clinical oral examination, sialometry |

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| Temporomandibular joint disorder | Definition:<br>Collection of conditions characterized by pain in the jaw muscles and/ or temporomandibular joint (TMJ) as well as surrounding structures, functional limitations in the TMJ or sounds (cracking, crepitation) from the TMJ. May be transient, recurrent or chronic.[29]<br><br>Grading source:<br>ALL-STAR research team.<br>Assessment of jaw muscles (palpation of the temporalis and masseter muscles) and joint pain (palpation and upon function); jaw movements (i.e., opening, lateral, and protrusive), functional and morphological dental occlusion.[29] | 1: Mild orofacial pain/TMD myalgia and or arthralgia.<br>2: Moderate orofacial pain/TMD myalgia and/or arthralgia.<br>3: Severe orofacial pain/TMD myalgia and/or arthralgia; medical and dental intervention needed.<br>4: Extensive TMD; may require surgical intervention.<br>5: Not applicable. | - Questionnaire and medical record validation<br>- Orofacial and dental evaluation |
| Dental maldevelopment | Definition:<br>A disorder characterized by pathological processes of the teeth occurring during tooth development. Includes: adontia, hypodontia, microdontia, root stunting, enamel demineralization/ decalcification etc.<br><br>Grading source:<br>CTCAEv4.03<br>Gastrointestinal disorders:<br>Tooth development disorder | 1: Asymptomatic; hypoplasia of teeth or enamel.<br>2: Impairment correctable with oral surgery.<br>3: Malformation with impairment not surgically correctable; disabling.<br>3: Not applicable.<br>4: Not applicable. | - Questionnaire and medical record validation<br>- Orofacial and dental evaluation |
| **NEUROLOGIC** | | | |
| **Health condition** | **Definition and Grading source** | **Grading** | **ALL-STAR data** |
| Autonomic dysfunction | Definition:<br>Disorder in the autonomic nerve system. Includes Horner's syndrome<br><br>Grading source:<br>St Jude modification of CTCAEv4.03<br>Nervous system disorders:<br>Other, specify | 1: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated<br>2: Moderate; minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental ADL<br>3: Severe or medically significant but not immediately life threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self-care ADL<br>4: Life-threatening consequences; urgent intervention indicated<br>5: Death | - Questionnaire, COMPASS31, and medical record validation<br>- Heart rate variability |

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| Cavernoma | Definition:<br>*A cluster of abnormal blood vessels usually found in the brain or spinal cord.*<br><br>Grading source:<br>CTCAEv4.03<br>Nervous system disorders:<br>Other, specify | 1: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated<br>2: Moderate; minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental ADL<br>3: Severe or medically significant but not immediately life threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self-care ADL<br>4: Life-threatening consequences; urgent intervention indicated<br>5: Death | - Questionnaire and medical record validation |
| Cerebellar dysfunction | Definition:<br>A disorder characterized by lack of coordination of muscle movements resulting in the impairment or inability to perform voluntary activities. Includes: demyelization, drug-induced, hereditary, nutritional, surgical, trauma, tumors, or vascular causes.<br><br>Grading source:<br>St Jude modification of CTCAEv4.03<br>Nervous system disorders:<br>Ataxia | 1: Asymptomatic; clinical or diagnostic observations only; intervention not indicated<br>2: Moderate symptoms; limiting instrumental ADL<br>3: Severe symptoms; limiting self-care ADL; mechanical assistance indicated<br>4 Not applicable<br>5: Not applicable | - Questionnaire and medical record validation |
| Cerebral necrosis | Definition:<br>A disorder characterized by a necrotic process occurring in the brain and/or spinal cord.<br><br>Grading source:<br>St Jude modification of CTCAEv4.03<br>Nervous system disorders:<br>Central nervous system necrosis | 1: Asymptomatic; clinical or diagnostic observations only; intervention not indicated<br>2: Moderate symptoms; corticosteroids indicated<br>3: Severe symptoms; medical intervention indicated (e.g., hyperbaric treatment of brain radiation necrosis)<br>4: Life-threatening consequences; urgent/surgical intervention indicated<br>5: Death | - Questionnaire and medical record validation |
| Cerebrovascular accident | Definition:<br>A disorder characterized by a sudden loss of sensory function due to an intracranial vascular event. Includes: lacunes, hemorrhagic stroke, Ischemic stroke.<br><br>Grading source:<br>St Jude modification of CTCAEv4.03<br>Nervous system disorders:<br>Stroke | 1: Asymptomatic or mild neurologic deficit; radiographic findings only<br>2: Moderate neurologic deficit<br>3: Severe neurologic deficit<br>4: Life-threatening consequences; urgent intervention indicated<br>5: Death | - Questionnaire and medical record validation |

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| Cerebrovascular disease | Definition:<br>Includes: stenotic or occlusive large vessel disease, moyamoya.<br><br>Grading source:<br>St Jude modification of CTCAEv4.03<br>Nervous system disorders:<br>Other, specify | 1: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated<br>2: Moderate; minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental ADL<br>3: Severe or medically significant but not immediately life threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self-care ADL<br>4: Life-threatening consequences; urgent intervention indicated<br>5: Death | - Questionnaire and medical record validation |
| Cranial nerve disorder | Definition:<br>A disorder characterized by involvement of a cranial nerve<br><br>Grading source:<br>St Jude modification of CTCAEv4.03<br>Nervous system disorders:<br>Trigeminal, oculomotor, etc. Cranial nerve disorder | 1: Asymptomatic; clinical or diagnostic observations only; intervention not indicated<br>2: Moderate symptoms; limiting instrumental ADL<br>3: Severe symptoms; limiting self-care ADL (e.g., surgical intervention indicated)<br>4: Not applicable<br>5: Not applicable | - Questionnaire and medical record validation |
| Dysarthria | Definition:<br>A disorder characterized by slow and slurred speech resulting from an inability to coordinate the muscles used in speech.<br><br>Grading source:<br>St Jude modification of CTCAEv4.03<br>Nervous system disorders:<br>Dysarthria | 1: Mild slurred speech (easily understood)<br>2: Moderate impairment of articulation or slurred speech (some need for repetition to be understood)<br>3: Severe impairment of articulation or slurred speech (unintelligible speech)<br>4: Not applicable<br>5: Not applicable | - Questionnaire and medical record validation |
| Generalized muscle weakness | Definition:<br>A disorder characterized by a reduction in the strength of muscles in multiple anatomic sites<br><br>Grading source:<br>ALL-STAR modification of CTCAEv4.03<br>Musculoskeletal and connective tissue disorders | 1: Symptomatic; weakness perceived by patient but not evident on physical exam<br>2: Symptomatic; weakness evident on physical exam; weakness limiting instrumental ADL<br>3: Weakness limiting self-care ADL; disabling; more than 2 SD below the expected mean (based on ALL-STAR control values)<br>4: Not applicable<br>5: Not applicable | - Questionnaire and medical record validation<br>- Physical tests |

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| Headaches, chronic/ recurrent | Definition:<br>Includes: migraines<br>Chronic headaches defined as headaches 15 days in a month for 3 consecutive months<br>Recurrent headaches defined as at least 5 headaches over lifetime<br><br>Grading source:<br>St Jude modification of CTCAEv4.03<br>Nervous system disorders:<br>Headaches<br><br>ALL-STAR modification: chronic/recurring headache is defined as more than one episode per week. Migraine included as diagnose independent of frequency. | 1: Mild pain<br>2: Moderate pain requiring prescriptive abortive medication; limiting instrumental ADL<br>3: Severe pain requiring prophylactic medication; limiting self-care ADL<br>4: Not applicable<br>5: Not applicable | - Questionnaire and medical record validation |
| Hydrocephalus | Definition:<br>A disorder characterized by an abnormal increase of cerebrospinal fluid in the ventricles of the brain.<br><br>Grading source:<br>CTCAEv4.03<br>Nervous system disorders:<br>Hydrocephalus | 1: Asymptomatic; clinical or diagnostic observations only; intervention not indicated<br>2: Moderate symptoms; intervention not indicated<br>3: Severe symptoms or neurological deficit; intervention indicated<br>4: Life-threatening consequences; urgent intervention indicated<br>5: Death | - Questionnaire and medical record validation |
| Hydrosyringomyelia | Definition: -<br>Includes: syrinx, syringohydromyelia, syringomyelia<br><br>Grading source:<br>St Jude modification of CTCAEv4.03<br>Nervous system disorders:<br>Other, specify | 1: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated<br>2: Moderate; minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental ADL<br>3: Severe or medically significant but not immediately life threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self-care ADL<br>4: Life-threatening consequences; urgent intervention indicated<br>5: Death | - Questionnaire and medical record validation |
| Intracranial hemorrhage | Definition:<br>A disorder characterized by bleeding from the cranium.<br>Includes: subdural, subarachnoid, intraventricular.<br><br>Grading source:<br>St Jude modification of CTCAEv4.03<br>Nervous system disorders:<br>Intracranial hemorrhage | 1: Asymptomatic; clinical or diagnostic observations only; intervention not indicated (MRI evidence of microhemorrhage, e.g. hemosiderin)<br>2: Moderate symptoms; medical intervention indicated<br>3: Ventriculostomy, ICP monitoring, intraventricular thrombolysis, or operative intervention indicated<br>4: Life-threatening consequences; urgent intervention indicated<br>5: Death | - Questionnaire and medical record validation |

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| Movement disorders | Definition:<br>A disorder characterized by uncontrolled and purposeless movements. Includes: athetosis, ballism, chorea, dystonia, myoclonus, opsoclonus/ myoclonus, Parkinsonism, restless legs, tic tremor, torticollis.<br><br>Grading source:<br>St Jude modification of CTCAEv4.03<br>Nervous system disorders:<br>Movements involuntary | 1: Mild involuntary movements<br>2: Moderate involuntary movements; limiting instrumental ADL<br>3: Severe involuntary movements; limiting self-care ADL<br>4: Not applicable<br>5: Not applicable | - Questionnaire and medical record validation |
| Multiple sclerosis | Definition:<br>An inflammatory disorder of the brain and spinal cord.[30]<br><br>Grading source:<br>St Jude modification of CTCAEv4.03<br>Nervous system disorders:<br>Other, specify | 1: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated<br>2: Moderate; minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental ADL<br>3: Severe or medically significant but not immediately life threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self-care ADL<br>4: Life-threatening consequences; urgent intervention indicated<br>5: Death | - Questionnaire and medical record validation |
| Narcolepsy | Definition:<br>A disorder characterized by characterized by excessive sleepiness during the daytime<br><br>Grading source:<br>St Jude modification of CTCAEv4.03<br>Nervous system disorders:<br>Hypersomnia | 1: Not applicable<br>2: Documentation of narcolepsy without need for therapy; moderate increased need for sleep<br>3: Documentation of narcolepsy with need for therapy; severe increased need for sleep<br>4: Not applicable<br>5: Not applicable | - Questionnaire and medical record validation |
| Nerve root disorder | Definition:<br>A disorder characterized by inflammation involving a nerve root. Patients experience marked discomfort radiating along a nerve path because of spinal pressure on the connecting nerve root. Includes: radiculopathy, plexopathy, cauda equina syndrome.<br><br>Grading source:<br>St Jude modification of CTCAEv4.03<br>Nervous system disorders:<br>Radiculitis | 1: Mild symptoms<br>2: Moderate symptoms; limiting instrumental ADL; medical intervention indicated<br>3: Severe symptoms; limiting self-care ADL<br>4: Life-threatening consequences; urgent intervention indicated<br>5: Death | - Questionnaire and medical record validation |

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| Neurogenic bladder | Definition:<br>Dysfunction of the lower urinary tract characterized by damage to the central nervous system (CNS), autonomic nervous system (ANS), or peripheral nervous system (PNS).[31]<br><br>Grading source:<br>St Jude modification of CTCAEv4.03<br>Nervous system disorders:<br>Other, specify | 1: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated<br>2: Moderate; minimal, local or noninvasive intervention indicated (medical management e.g., oxybutynin); limiting age appropriate instrumental ADL<br>3: Severe or medically significant but not immediately life threatening; hospitalization or prolongation of existing hospitalization indicated; surgical intervention indicated (e.g. ileal-anal pouch); disabling; limiting self-care ADL<br>4: Life-threatening consequences; urgent intervention indicated<br>5: Death | - Questionnaire, COMPASS31, and medical record validation |
| Neurogenic bowel | Definition:<br>Dysfunction of the bowel characterized by damage to the central nervous system (CNS), autonomic nervous system (ANS), or peripheral nervous system (PNS).[32]<br><br>Grading source:<br>St Jude modification of CTCAEv4.03<br>Nervous system disorders:<br>Other, specify | 1: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated<br>2: Moderate; minimal, local or noninvasive intervention indicated (e.g. stool softener); limiting age appropriate instrumental ADL<br>3: Severe or medically significant but not immediately life threatening; hospitalization or prolongation of existing hospitalization indicated; surgical intervention indicated (e.g. MACE); disabling; limiting self-care ADL<br>4: Life-threatening consequences; urgent intervention indicated<br>5: Death | - Questionnaire and medical record validation |
| Neuromuscular disorders | Definition:<br>Includes: dermatomyositis, myotonia, neuromuscular disorder, polymyositis, rhabdomyolysis, steroid myopathy, critical illness myopathy/neuropathy<br><br>Grading source:<br>St Jude modification of CTCAEv4.03<br>Nervous system disorders:<br>Other, specify | 1: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated<br>2: Moderate; minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental ADL<br>3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self-care ADL<br>4: Life-threatening consequences; urgent intervention indicated<br>5: Death | - Questionnaire and medical record validation |
| Paralytic disorder | Definition:<br>Includes: hemiparesis/ plegia, quadriparesis/ plegia, parapareis/ plegia, flaccid paralysis, spastic paralysis<br><br>Grading source:<br>St Jude modification of CTCAEv4.03<br>Nervous system disorders:<br>Other, specify | 1: Asymptomatic or mild symptoms (e.g., facial paraparesis); clinical or diagnostic observations only; intervention not indicated<br>2: Moderate (e.g., paraparesis); minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental ADL<br>3: Severe weakness or sensory loss (e.g., paraplegia requiring wheelchair); limiting self-care ADL<br>4: Life-threatening consequences (e.g., quadriplegia); urgent intervention indicated<br>5: Death | - Questionnaire and medical record validation |

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| Peripheral motor neuropathy | Definition:<br>A disorder characterized by inflammation or degeneration of the peripheral motor nerves.<br>Includes: inflammatory demyelinating polyneuropathy disorder - Guillain-Barre syndrome.<br><br>Grading source:<br>CTCAEv4.03<br>Nervous system disorders:<br>Peripheral motor neuropathy | 1: Asymptomatic; clinical or diagnostic observations only; intervention not indicated<br>2: Moderate symptoms; limiting instrumental ADL<br>3: Severe symptoms; limiting self- care ADL; assistive device indicated<br>4: Life-threatening consequences; urgent intervention indicated<br>5: Death | - Questionnaire and medical record validation<br>- Neurological evaluation according to TNS including electroneurography. |
| Peripheral sensory neuropathy | Definition:<br>A disorder characterized by inflammation or degeneration of the peripheral sensory nerves.<br><br>Grading source:<br>CTCAEv4.03<br>Nervous system disorders:<br>Peripheral sensory neuropathy | 1: Asymptomatic; loss of deep tendon reflexes or paresthesia<br>2: Moderate symptoms; limiting instrumental ADL<br>3: Severe symptoms; limiting self-care ADL<br>4: Life-threatening consequences; urgent intervention indicated<br>5: Death | - Questionnaire and medical record validation<br>- Neurological evaluation according to TNS including electroneurography. |
| Pseudomeningocele | Definition:<br>An accumulation of cerebrospinal fluid in the extradural space due to a fault in the dural arachnoid layer.[33]<br><br>Grading source:<br>ST Jude modification of CTCAEv4.03<br>Nervous system disorders:<br>Other, specify | 1: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated<br>2: Moderate; minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental ADL<br>3: Severe or medically significant but not immediately life threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self-care ADL<br>4: Life-threatening consequences; urgent intervention indicated<br>5: Death | - Questionnaire and medical record validation |
| Pseudotumor cerebri | Definition:<br>A syndrome with increased intracranial pressure without a space-occupying lesion.[34]<br><br>Grading source:<br>ST Jude modification of CTCAEv4.03<br>Nervous system disorders:<br>Other, specify | 1: Asymptomatic or mild symptoms; clinical management or diagnostic observations only (e.g., weight control)<br>2: Moderate; minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental ADL; medical intervention indicated or initiated (e.g., acetazolamide)<br>3: Severe or medically significant but not immediately life threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self-care ADL; surgical intervention indicated or initiated (e.g., lumbar puncture)<br>4: Life-threatening consequences; urgent intervention indicated (e.g., severe visual impairment)<br>5: Death | - Questionnaire and medical record validation |

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| Seizures | Definition:<br>A transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain.[35]<br><br>Grading source:<br>St Jude category and grading according to multidisciplinary team consensus | 1: Seizures not requiring medication<br>2: Seizures requiring one non-prn medication<br>3: Seizures requiring two or more non-prn medications; poorly controlled seizures with prescribed medications<br>4: Seizures requiring evaluation for surgical intervention<br>5: Death | - Questionnaire and medical record validation |
| **OCULAR/VISUAL** | | | |
| **Health condition** | **Definition and Grading source** | **Grading** | **ALL-STAR data** |
| Cataract | Definition:<br>A disorder characterized by partial or complete opacity of the crystalline lens of one or both eyes. This results in a decrease in visual acuity and eventual blindness if untreated.<br><br>Grading source:<br>St Jude modification of CTCAEv4.03<br>Eye disorders:<br>Cataract | 1: Asymptomatic; clinical or diagnostic observations only; intervention not indicated (20/30 or better)<br>2: Symptomatic; moderate decrease in visual acuity (20/40 or better)<br>3: Symptomatic with marked decrease in visual acuity (worse than 20/40 but better than 20/200); operative intervention indicated (e.g., cataract surgery)<br>4: Blindness (20/200 or worse) in the affected eye<br>5: Not applicable | - Questionnaire and medical record validation |
| Diplopia | Definition:<br>*Double vision*<br><br>Grading source:<br>St Jude modification of CTCAEv4.03<br>Eye disorders:<br>Other, specify | 1: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated<br>2: Moderate; minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental ADL<br>3: Severe or medically significant but not immediately sight threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self-care ADL<br>4: Not applicable<br>5: Not applicable | - Questionnaire and medical record validation |
| Dry eye syndrome | Definition:<br>Includes: Keratitis sicca, xerophthalmia, kerato-conjunctivitis sicca, Sjogren's syndrome, lacrimal duct atrophy, limbal stem cell deficiency.<br><br>Grading source:<br>St Jude modification of CTCAEv4.03<br>Eye disorders:<br>Other, specify | 1: Asymptomatic; clinical or diagnostic observations only; mild symptoms relieved by lubricants<br>2: Symptomatic; multiple agents indicated; limiting instrumental ADL<br>3: Decrease in visual acuity (<20/40); limiting self-care ADL<br>4: Not applicable<br>5: Not applicable | - Questionnaire, COMPASS31 and medical record validation |

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| Eyelid function disorder | Definition:<br>Includes: entropion, ectropion, lagophthalmos, ptosis<br><br>Grading source:<br>St Jude modification of CTCAEv4.03<br>Eye disorders:<br>Other, specify | 1: Asymptomatic; clinical or diagnostic observations only; intervention not indicated<br>2: Symptomatic; non-operative intervention indicated; limiting instrumental ADL<br>3: Limiting self-care ADL; operative intervention indicated<br>4: Not applicable<br>5: Not applicable | - Questionnaire and medical record validation |
| Glaucoma | Definition:<br>A disorder characterized by an increase in pressure in the eyeball due to obstruction of the aqueous humor outflow<br><br>Grading source:<br>CTCAEv4.03<br>Eye disorders:<br>Glaucoma | 1: Elevated intraocular pressure (EIOP) with single topical agent for intervention; no visual field deficit<br>2: EIOP causing early visual field deficits; multiple topical or oral agents indicated; limiting instrumental ADL<br>3: EIOP causing marked visual field deficits (e.g., involving both superior and inferior visual fields); operative intervention indicated; limiting self-care ADL<br>4: Blindness (20/200 or worse) in the affected eye<br>5: Not applicable | - Questionnaire and medical record validation |
| Ocular disease, noninfectious | Definition:<br>Includes: chorioretinitis, uveitis, iritis, scleritis<br><br>Grading source:<br>St Jude modification of CTCAEv4.03<br>Eye disorders:<br>Other, specify | 1: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated<br>2: Moderate; minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental ADL<br>3: Severe or medically significant but not immediately sight threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self-care ADL<br>4: Sight-threatening consequences; urgent intervention indicated; blindness (20/200 or worse) in the affected eye<br>5: Not applicable | - Questionnaire and medical record validation |
| Ocular surface disease | Definition:<br>A disorder characterized by inflammation to the cornea of the eye<br><br>Grading source:<br>St Jude modification of CTCAEv4.03<br>Eye disorders:<br>Keratitis | 1: Not applicable<br>2: Symptomatic; medical intervention indicated (e.g., topical agents); limiting instrumental ADL<br>3: Decline in vision (worse than 20/40 but better than 20/200); limiting self-care ADL<br>4: Perforation or blindness (20/200 or worse) in the affected eye<br>5: Not applicable | - Questionnaire and medical record validation |
| Photophobia | Definition:<br>A disorder characterized by fear and avoidance of light.<br><br>Grading source:<br>CTCAEv4.03<br>Eye disorders:<br>Photophobia | 1: Symptomatic but not limiting ADL<br>2: Limiting instrumental ADL<br>3: Limiting self-care ADL<br>4: Not applicable<br>5: Not applicable | - Questionnaire, COMPASS31 and medical record validation |

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| Phthisis bulbi | Definition:<br>Blind, painful eye<br><br>Grading source:<br>St Jude modification of CTCAEv4.03<br>Eye disorders<br>Eye pain | 1: Mild pain<br>2: Moderate pain; limiting instrumental ADL<br>3: Severe pain; limiting self-care ADL<br>4: Not applicable<br>5: Not applicable | - Questionnaire and medical record validation |
| Retinal detachment | Definition:<br>A disorder characterized by the separation of the inner retina layers from the underlying pigment epithelium.<br><br>Grading source:<br>St Jude modification of CTCAEv4.03<br>Eye disorders:<br>Retinal detachment | 1: Asymptomatic<br>2: Rhegmatogenous or exudative and visual acuity 20/40 or better<br>3: Rhegmatogenous or exudative detachment; operative intervention indicated; decline in vision (worse than 20/40 but better than 20/200)<br>4: Blindness (20/200 or worse) in the affected eye<br>5: Not applicable | - Questionnaire and medical record validation |
| Retinopathy | Definition:<br>A disorder involving the retina.<br><br>Grading source:<br>CTCAEv4.03<br>Eye disorders:<br>Retinopathy | 1: Asymptomatic; clinical or diagnostic observations only<br>2: Symptomatic with moderate decrease in visual acuity (20/40 or better); limiting instrumental ADL<br>3: Symptomatic with marked decrease in visual acuity (worse than 20/40); disabling; limiting self-care ADL<br>4: Blindness (20/200 or worse) in the affected eye<br>5: Not applicable | - Questionnaire and medical record validation |
| Strabismus | Definition:<br>Includes: esotropia, exotropia, hypertropia, Parinaud's syndrome, Internuclear ophthalmoplegia<br><br>Grading source:<br>St Jude modification of CTCAEv4.03<br>Eye disorders:<br>Other, specify | 1: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated<br>2: Moderate; minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental ADL<br>3: Severe or medically significant but not immediately sight threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self-care ADL<br>4: Sight-threatening consequences; urgent intervention indicated; blindness (20/200 or worse) in the affected eye<br>5: Not applicable | - Questionnaire and medical record validation |
| Visual acuity, reduced (OD) | Definition:<br>A disorder characterized by involvement of the optic nerve (second cranial nerve).<br><br>Grading source:<br>St Jude modification of CTCAEv4.03<br>Eye disorders:<br>Optic nerve disorder | 1: Asymptomatic; clinical or diagnostic observations only (reduced visual acuity corrected to 20/40 or better)<br>2: Limiting vision of the affected eye (reduced visual acuity corrected to less than 20/40 but better than 20/60)<br>3: Limiting vision in the affected eye (reduced visual acuity corrected to 20/60 but better than 20/200)<br>4: Blindness (corrected to 20/200 or worse, includes count fingers, hand motion, light perception only) in the affected eye (cortical blindness, enucleation)<br>5: Not applicable | - Questionnaire and medical record validation |

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| Visual acuity, reduced (OS) | Definition:<br>A disorder characterized by involvement of the optic nerve (second cranial nerve).<br><br>Grading source:<br>St Jude modification of CTCAEv4.03<br>Eye disorders:<br>Optic nerve disorder | 1: Asymptomatic; clinical or diagnostic observations only (reduced visual acuity corrected to 20/40 or better)<br>2: Limiting vision of the affected eye (reduced visual acuity corrected to less than 20/40 but better than 20/60)<br>3: Limiting vision in the affected eye (reduced visual acuity corrected to 20/60 but better than 20/200)<br>4: Blindness (corrected to 20/200 or worse, includes count fingers, hand motion, light perception only) in the affected eye (cortical blindness, enucleation)<br>5: Not applicable | - Questionnaire and medical record validation |
| Visual field deficit | Definition:<br>*Partly or total loss of usual visual field.*<br><br>Grading source:<br>St Jude modification of CTCAEv4.03<br>Eye disorders:<br>Optic nerve disorder | 1: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated<br>2: Moderate; minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental ADL (can't drive)<br>3: Severe or medically significant but not immediately sight threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self-care ADL (can't ambulate/navigate)<br>4: Not applicable<br>5: Not applicable | - Questionnaire and medical record validation |
| **PULMONARY** | | | |
| **Health condition** | **Definition and Grading source** | **Grading** | **ALL-STAR data** |
| Asthma | Definition:<br>A disorder characterized by a sudden contraction of the smooth muscles of the bronchial wall. Based on physician diagnosis by appropriate clinical signs and symptoms, reversible airway obstruction.<br><br>Grading source:<br>St Jude modification of CTCAEv4.03<br>Respiratory, thoracic and mediastinal disorders:<br>Bronchospasm | 1: Mild symptoms; intervention not Indicated<br>2: Symptomatic; medical intervention indicated; limiting instrumental ADL; intermittent asthma requiring short-acting beta agonists as needed<br>3: Limiting self-care ADL; oxygen saturation decreased; persistent asthma requiring daily controller medication (oral or inhaled)<br>4: Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated<br>5: Death | - Questionnaire and medical record validation<br>- Lung function tests |

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| Chronic obstructive pulmonary disease (COPD) | Definition:<br>Based on physician diagnosis by appropriate clinical signs and symptoms, irreversible airway obstruction; includes emphysema, chronic bronchitis, and mixed chronic obstructive asthma/COPD syndrome.<br><br>Grading source:<br>St Jude modification of CTCAEv4.03<br>Respiratory, thoracic and mediastinal disorders:<br>Other, specify | 1: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated<br>2: Moderate; minimal, local or noninvasive intervention indicated or initiated (inhaled medications); limiting age-appropriate instrumental ADL<br>3: Severe or medically significant but not immediately life-threatening (e.g., requiring supplementation of oxygen, systemic corticosteroids, BIPAP, or CPAP); hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self-care ADL<br>4: Life-threatening consequences; urgent intervention indicated<br>5: Death | - Questionnaire and medical record validation<br>- Lung function tests |
| Epistaxis, chronic/recurrent | Definition:<br>Defined as 3 events in last 6 months<br><br>Grading Source:<br>CTCAEv4.03<br>Respiratory, thoracic and mediastinal disorders:<br>Epistaxis | 1: Mild symptoms; intervention not Indicated<br>2: Moderate symptoms; medical intervention indicated (e.g., nasal packing, cauterization; topical vasoconstrictors)<br>3: Transfusion, radiologic, endoscopic, or operative intervention indicated (e.g., hemostasis of bleeding site)<br>4: Life-threatening consequences; urgent intervention indicated<br>5: Death | - Questionnaire and medical record validation |
| Obstructive sleep apnea | Definition:<br>A condition with narrowing or collapse of the throat causing repeatedly obstructive sleep apnoea events.[36]<br><br>Grading source:<br>St Jude category and grading according to multidisciplinary team consensus | 1: Documentation of apnea; no need for medication<br>2: Documentation of mild apnea; behavioral intervention initiated or indicated<br>3: Documentation of moderate apnea; CPAP initiated or indicated<br>4: Documentation of severe apnea with secondary complications (CHF, HTN, headache)<br>5: Not applicable | - Questionnaire and medical record validation |

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| Obstructive ventilatory defect | Definition:<br>Defined by FEV1 < 80% predicted and <LLN. Disorders associated with this pattern and reduced FEV1/FVC ratio (obstructive ventilatory defect) include: asthma, COPD, tracheobronchomalacia, obliterative bronchiolitis and bronchiectasis. Disorders associated with this pattern and normal or increased FEV1/FVC (possible restrictive ventilatory defect, confirm with TLC) include pulmonary fibrosis, other interstitial lung diseases, chest wall disorders)<br><br>Grading source;<br>New category and Grading source introduced by St Jude:<br><br>Pellegrino et al, Interpretative strategies for lung function tests. Eur Resp J 2005;26:948-968. Table 6 | 1: FEV1 (percentages of observed FEV1 related to its predicted value): 79-70% predicted<br>2: FEV1: 69-50% predicted<br>3: FEV1: 49-35% predicted<br>4: FEV1: <35% predicted<br>5: Not applicable | - Questionnaire and medical record validation<br>- Lung function tests |
| Pleural space disorders | Definition:<br>Includes: pleural effusions, chylothorax, hemothorax<br><br>Grading source:<br>St Jude modification of CTCAEv4.03<br>Respiratory, thoracic and mediastinal disorders<br>Pneumothorax | 1: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated<br>2: Moderate to severe symptoms and non-operative intervention indicated (e.g., tube placement without sclerosis)<br>3: Sclerosis and/or operative intervention indicated; hospitalization indicated<br>4: Life-threatening consequences; urgent intervention indicated<br>5: Death | - Questionnaire and medical record validation |
| Pneumonitis | Definition:<br>A disorder characterized by inflammation focally or diffusely affecting the lung parenchyma.<br><br>Grading source:<br>St Jude modification of CTCAEv4.03<br>Respiratory, thoracic and mediastinal disorders:<br>Pneumonitis | 1: Not applicable<br>2: Symptomatic; medical intervention indicated; limiting instrumental ADL<br>3: Severe symptoms; limiting self-care ADL; oxygen indicated<br>4: Life-threatening respiratory compromise; urgent intervention indicated (e.g., tracheotomy or intubation)<br>5: Death | - Questionnaire and medical record validation |

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| Pulmonary diffusion defect | Definition:<br>DLCOcorr < 75%<br>predicted and <LLN. Includes: pneumonitis, pulmonary fibrosis, other interstitial lung diseases, pulmonary vascular disorders and emphysema)<br><br>Grading source:<br>New category and Grading source introduced by St Jude:<br><br>Pellegrino et al, Interpretative strategies for lung function tests. Eur Resp J 2005;26:948-968. Table 14 | 1: DLCO: 74-60% predicted<br>2: DLCO: <60%-40% predicted<br>3: DLCO: <40% predicted<br>4: Not applicable<br>5: Not applicable | - Questionnaire and medical record validation<br>- Lung function tests |
| Pulmonary embolism | Definition:<br>A disorder characterized by occlusion of a vessel by a thrombus that has migrated from a distal site via the blood stream.<br><br>Grading source:<br>St Jude modification of CTCAEv4.03<br>Vascular disorders:<br>Thromboembolic event | 1: Not applicable<br>2: Not applicable<br>3: Urgent medical intervention indicated<br>4: Life-threatening with hemodynamic or neurologic instability<br>5: Death | - Questionnaire and medical record validation |
| Respiratory tract hemorrhage | Definition:<br>A disorder characterized by bleeding from the bronchial wall and/or lung parenchyma.<br><br>Grading source:<br>St Jude modification of CTCAEv4.03<br>Respiratory, thoracic and mediastinal disorders:<br>Bronchopulmonary hemorrhage | 1: Mild symptoms; intervention not Indicated<br>2: Moderate symptoms; medical intervention indicated<br>3: Transfusion, radiologic, endoscopic, or operative intervention indicated (e.g., hemostasis of bleeding site)<br>4: Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated<br>5: Death | - Questionnaire and medical record validation |

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| Restrictive ventilatory defect | Definition:<br>Defined by TLC < 75% predicted and <LLN. Includes: pulmonary fibrosis and other interstitial lung disease, pneumonitis, chest wall disorders.<br><br>Grading source:<br>New category and Grading source introduced by St Jude:<br><br>American Thoracic Society, Lung Function Testing: Selection of Reference Values and Interpretative Strategies. Am Rev Respir Dis 1991;144:1202-1218. Table 13 | 1: TLC: 74 -70%<br>2: TLC: 69 - 60% predicted; limiting instrumental ADL<br>3: TLC: <60% predicted; limiting self-care ADL<br>4: Not applicable<br>5: Not applicable | - Questionnaire and medical record validation<br>- Lung function tests |
| Tracheal aspiration | Definition:<br>A disorder characterized by inhalation of solids or liquids into the lungs.<br><br>Grading source:<br>ST Jude modification of CTCAEv4.03 Respiratory, thoracic and mediastinal disorders:<br>Aspiration | 1: Asymptomatic; clinical or diagnostic observations only; intervention not indicated<br>2: Altered eating habits; coughing or choking episodes after eating or swallowing; medical intervention indicated (e.g., suction or oxygen)<br>3: Dyspnea and pneumonia symptoms (e.g., aspiration pneumonia); hospitalization indicated; unable to aliment orally<br>4: Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated<br>5: Death | - Questionnaire and medical record validation |
| Tracheal stenosis | Definition:<br>A disorder characterized by a narrowing of the trachea.<br><br>Grading source:<br>CTCAEv4.03 Respiratory, thoracic and mediastinal disorders:<br>Tracheal stenosis | 1: Asymptomatic; clinical or diagnostic observations only; intervention not indicated<br>2: Symptomatic (e.g., noisy airway breathing), but causing no respiratory distress; medical management indicated (e.g., steroids)<br>3: Stridor or respiratory distress limiting self-care ADL; endoscopic intervention indicated (e.g., stent, laser)<br>4: Life-threatening airway compromise; urgent intervention indicated (e.g., tracheotomy or intubation)<br>5: Death | - Questionnaire and medical record validation |

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| PSYCHIATRIC | | | |
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| **Health condition** | **Definition and Grading source** | **Grading** | **ALL-STAR data** |
| Anxiety | Definition:<br>Validated patient reported outcome measure**.** Threshold of clinical intervention and impact on ADL<br><br>Grading source:<br>St Jude<br>*"Detailed grading criteria for neuropsychological outcomes were outlined by psychologists incorporating patient-reported outcomes and the results of validated cognitive and psychological measures and comprehensive psychosocial evaluations by study social workers".*[1]<br><br>ALL-STAR modification: Diagnosed by psychiatrist. | 1: Score >1 SD above the mean and mental health intervention not indicated.<br>2: Score >1.5 SD above the mean; Score ≤1.5 SD above the mean and treatment limited to 1 initiated or indicated mental health intervention; symptoms interfere with social or occupational functioning<br>3: Score >2 SD above the mean; Score ≤2 SD and >1.5 SD above the mean and >1 mental health intervention initiated or indicated; symptoms interfere with self-care<br>4: Hospitalization due to symptoms of anxiety indicated<br>5: Death | - Questionnaire and medical record validation |
| Depression | Definition:<br>Validated patient reported outcome measure<br>Threshold of clinical intervention and impact on ADL<br><br>Grading source:<br>St Jude<br>*"Detailed grading criteria for neuropsychological outcomes were outlined by psychologists incorporating patient-reported outcomes and the results of validated cognitive and psychological measures and comprehensive psychosocial evaluations by study social workers".*[1]<br><br>ALL-STAR modification: Diagnosed by psychiatrist. | 1: Score >1 SD above the mean and mental health intervention not indicated<br>2: Score >1.5 SD above the mean; Score ≤1.5 SD above the mean and treatment limited to 1 initiated or indicated mental health intervention; symptoms interfere with social or occupational functioning<br>3: Score >1.5 above the mean and patient reports suicide ideation; Score >2 SD above the mean; Score ≤2 SD and >1.5 SD above the mean and >1 mental health intervention initiated or indicated; symptoms interfere with self-care<br>4: Hospitalization due to symptoms of depression indicated<br>5: Death | - Questionnaire and medical record validation |

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| Other psychiatric disorders | Definition<br>A disorder characterized by personality change, impaired functioning, and loss of touch with reality. It may be a manifestation of schizophrenia, bipolar disorder or brain tumor.<br>E.g., delirium; delusions; hallucinations; paranoia; psychosis<br><br>Grading source:<br>St Jude modification of CTCAEv4.03<br>Psychiatric: Psychosis<br><br>ALL-STAR modification: Diagnosed by psychiatrist. | 1: Mild symptoms reported, and mental health intervention not indicated<br>2: Moderate symptoms reported; treatment limited to 1 initiated or indicated mental health intervention; symptoms interfere with social or occupational functioning<br>3: Severe symptoms reported; >1 mental health intervention initiated or indicated; symptoms interfere with self-care<br>4: Hospitalization or urgent intervention due to symptoms is indicated<br>5: Death | - Questionnaire and medical record validation |
| **RENAL / URINARY** | | | |
| **Health condition** | **Definition and Grading source** | **Grading** | **ALL-STAR data** |
| Acute kidney injury | Definition:<br>A disorder characterized by the acute loss of renal function and is traditionally classified as pre-renal (low blood flow into kidney), renal (kidney damage) and postrenal causes (ureteral or bladder outflow obstruction).<br><br>Grading source:<br>St Jude modification of CTCAEv4.03<br>Renal and urinary disorders:<br>Acute kidney injury | 1: Creatinine 1.5-2.0 x above age-specific ULN<br>2: Creatinine 2 - 3 x above age-specific ULN<br>3: Creatinine >3 x age-specific ULN or >4.0 mg/dL; hospitalization indicated<br>4: Life-threatening consequences; dialysis indicated<br>5: Death | - Questionnaire and medical record validation<br>- Creatinine<br>- Cystatin-C<br>- eGFR |
| Chronic hematuria | Definition: A disorder characterized by laboratory test results that indicate blood in the urine. Defined as > 5 RBCs/hpf documented on more than one urinalysis.<br><br>Grading source:<br>St Jude modification of CTCAEv4.03<br>Renal and urinary disorders:<br>Hematuria | 1: Asymptomatic; clinical or diagnostic observations only; intervention not indicated<br>2: Symptomatic; urinary catheter or bladder irrigation indicated; limiting instrumental ADL<br>3: Gross hematuria; transfusion, IV medications or hospitalization indicated; elective invasive intervention indicated; limiting self-care ADL<br>4: Life-threatening consequences; urgent invasive intervention indicated<br>5: Death | - Questionnaire and medical record validation |

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| Chronic kidney disease | Definition:<br>A disorder characterized by gradual and usually permanent loss of kidney function resulting in renal failure. Includes CKD requiring dialysis/transplant<br><br>Grading source:<br>St Jude modification of CTCAEv4.03<br>Renal and urinary disorders:<br>Chronic kidney disease<br><br>eGFR estimated used in the KDIGO estimating equations:<br>http://www.kdigo.org/clinical_practice_guidelines/pdf/CKD/KDIGO_2012_CKD_GL.pdf<br><br>ALL-STAR modification: eGFR estimated according to CKiDkrea-cysC-equation in children[37] and CKD-EPI$_{crea}$-equation in adults[38]. | 1: eGFR (estimated Glomerular Filtration Rate) or CrCl (creatinine clearance) <LLN – 60 ml/min/1.73 m$^2$ AND proteinuria 1+ present; urine protein/creatinine >0.5<br>2: eGFR or CrCl 59-30 ml/min/1.73 m$^2$; medication (e.g., electrolytes, ACE inhibition, etc….) indicated or initiated<br>3: eGFR or CrCl 29-15 ml/min/1.73 m$^2$<br>4: eGFR or CrCl <15 ml/min/1.73 m$^2$; dialysis or renal transplant indicated or initiated/performed<br>5: Death | - Questionnaire and medical record validation<br>- eGFR |
| Incontinence | Definition:<br>A disorder characterized by inability to control the flow of urine from the bladder.<br><br>Grading source:<br>CTCAEv4.03<br>Renal and urinary disorders:<br>Urinary incontinence | 1: Occasional (e.g., with coughing, sneezing, etc.), pads not indicated<br>2: Spontaneous; pads indicated; limiting instrumental ADL<br>3: Intervention indicated (e.g., clamp, collagen injections); operative intervention indicated; limiting self-care ADL<br>4: Not applicable<br>5: Not applicable | - Questionnaire and medical record validation |
| Obstructive uropathy | Definition:<br>A disorder characterized by blockage of the normal flow of contents of the urinary tract. Includes: urinary tract stenosis; urinary tract stricture.<br><br>Grading source:<br>St Jude modification of CTCAEv4.03<br>Renal and urinary disorders:<br>Urinary tract obstruction | 1: Asymptomatic; clinical or diagnostic observations only<br>2: Symptomatic but no hydronephrosis, sepsis or renal dysfunction; urethral dilation, urinary or suprapubic catheter indicated<br>3: Symptomatic and altered organ function (e.g., hydronephrosis, or renal dysfunction); elective invasive intervention indicated<br>4: Life-threatening consequences; urgent invasive intervention indicated<br>5: Death | - Questionnaire and medical record validation |

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| Urinary bladder dysfunction | Definition:<br>A disorder characterized by a sudden compelling urge to urinate. Includes: dysfunctional voiding, hypertonic bladder, urinary frequency, urinary hesitancy.<br><br>Grading source<br>St Jude modification of CTCAEv4.03<br>Renal and urinary disorders:<br>Urinary frequency<br>Urinary urgency | 1: Present<br>2: Limiting instrumental ADL; medical management indicated or initiated<br>3: Surgical management indicated or initiated (e.g., trans-electrical nerve stimulation, sacral neural modulation)<br>4: Not applicable<br>5: Not applicable | - Questionnaire and medical record validation |
| Urinary tract calculi | Definition:<br>A disorder characterized by the formation of crystals in the pelvis of the kidney. Includes: renal calculi, bladder stone/calculi, ureteral calculi.<br><br>Grading source:<br>St Jude modification of CTCAEv4.03<br>Renal and urinary disorders:<br>Renal calculi | 1: Asymptomatic or mild symptoms; occasional use of nonprescription analgesics indicated<br>2: Symptomatic; oral antiemetics indicated; around the clock nonprescription analgesics or any oral narcotic analgesics indicated<br>3: Hospitalization indicated; IV intervention (e.g., analgesics, antiemetics); elective invasive intervention indicated<br>4: Life-threatening consequences; urgent invasive intervention indicated<br>5: Death | - Questionnaire and medical record validation |
| Vesicoureteral reflux, acquired | Definition:<br>Abnormal retrograde flow of urine from the bladder to the ureter and potentially the kidney.[39]<br><br>Grading source:<br>St Jude modification of CTCAEv4.03<br>Renal and urinary disorders:<br>Other, specify | 1: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated<br>2: Moderate, local or noninvasive intervention indicated; limiting instrumental ADL<br>3: Severe or medically significant but not immediately life threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self-care ADL<br>4: Life-threatening consequences; urgent intervention indicated<br>5: Death | - Questionnaire and medical record validation |
| **REPRODUCTIVE / GENITAL** | | | |
| **Health condition** | **Definition and Grading source** | **Grading** | **ALL-STAR data** |
| Abnormal sperm concentration<br><br>(Includes: oligospermia, azoospermia) | Definition:<br>A disorder characterized by a decrease or complete absence of spermatozoa in the semen.<br><br>St Jude modification of<br>Reproductive system and breast disorders:<br>Oligospermia<br>Azoospermia | 1: Not applicable<br>2: Sperm concentration > 0 but < 15 million spermatozoa/mL<br>3: Absence of sperm in ejaculate<br>4: Not applicable<br>5: Not applicable | - Questionnaire and medical record validation |

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| Cervical dysplasia | Definition:<br>Abnormal growth of cells on the surface of the cervix.[40]<br><br>Grading source:<br>St Jude modification of<br>CTCAE v4.03<br>Reproductive system and breast disorder:<br>Other, specify | 1: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated<br>2: Moderate; minimal, local or non-invasive intervention indicated; limiting age appropriate instrumental ADL (e.g., colposcopy)<br>3: Severe or medically significant but not immediately life threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self-care ADL (e.g., conization for carcinoma-in-situ)<br>4: Not applicable<br>5: Not applicable | - Questionnaire and medical record validation |
| Dysfunctional uterine bleeding | Definition:<br>A disorder characterized by abnormally heavy vaginal bleeding during menses.<br><br>Grading source:<br>CTCAE v4.03<br>Reproductive system and breast disorders<br>Menorrhagia | 1: Mild; iron supplements indicated<br>2: Moderate symptoms; medical intervention indicated (e.g., hormones)<br>3: Severe; transfusion indicated; surgical intervention indicated (e.g., hysterectomy)<br>4: Life-threatening consequences; urgent intervention indicated<br>5: Death | - Questionnaire and medical record validation |
| Endometriosis | Definition:<br>The presence of endometrial tissue outside the uterine cavity.[41]<br><br>Grading source:<br>St Jude modification of<br>CTCAE v4.03<br>Reproductive system and breast disorders:<br>Other, specify | 1: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated<br>2: Moderate; minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental ADL (e.g., medical management)<br>3: Severe or medically significant but not immediately life threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self-care ADL (e.g., surgical intervention)<br>4: Life-threatening consequences; urgent intervention indicated<br>5: Death | - Questionnaire and medical record validation |
| Erectile dysfunction | Definition:<br>A disorder characterized by the persistent or recurrent inability to achieve or to maintain an erection during sexual activity.<br><br>Grading source:<br>CTCAE v4.03<br>Reproductive system and breast disorders:<br>Erectile dysfunction | 1: Decrease in erectile function (frequency or rigidity of erections) but intervention not indicated (e.g., medication or use of mechanical device, penile pump)<br>2: Decrease in erectile function (frequency/ rigidity of erections), erectile intervention indicated, (e.g., medication or mechanical devices such as penile pump)<br>3: Decrease in erectile function (frequency/ rigidity of erections) but erectile intervention not helpful (e.g., medication or mechanical devices such as penile pump); placement of a permanent penile prosthesis indicated (not previously present)<br>4: Not applicable<br>5: Not applicable | - Questionnaire and medical record validation |
| Genitourinary adhesions | Definition:<br>*Intraabdominal formation of fibrous bands between genital and urinary organs*.<br><br>Grading source:<br>St Jude modification of CTCAE v4.03<br>Reproductive system and breast disorders:<br>Other, specify | 1: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated<br>2: Moderate; minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental ADL<br>3: Severe or medically significant but not immediately life threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self-care ADL<br>4: Life-threatening consequences; urgent intervention indicated<br>5: Death | - Questionnaire and medical record validation |

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|---|---|---|---|
| Hypogonadism, central (hypogonadotropic) | Definition:<br>A finding based on laboratory test results that indicate abnormal levels of gonadotrophin hormone in a blood specimen.<br><br>Grading source:<br>St Jude modification of<br>CTCAE v4.03<br>Investigations:<br>Blood gonadotropin abnormal | 1: Asymptomatic; clinical or diagnostic observations only; intervention not indicated<br>2: Symptomatic; medical intervention indicated or initiated; limiting instrumental ADL<br>3. Severe symptoms; medical intervention indicated or initiated; limiting self-care ADL<br>4. Not applicable<br>5. Not applicable | - Questionnaire and medical record validation<br>- FSH<br>- LH<br>- Testosterone<br>- SHBG |
| Leydig cell insufficiency | Definition:<br>Leydig cell failure resulting from damage or loss of the machinery required for testosterone synthesis and release.[42]<br><br>Grading source:<br>St Jude modification of<br>CTCAE v4.03<br>Reproductive system and breast disorders:<br>Other, specify | 1: Asymptomatic; clinical or diagnostic observations only; intervention not indicated<br>2: Symptomatic; medical intervention indicated or initiated; limiting instrumental ADL<br>3: Severe symptoms; medical intervention indicated or initiated; limiting self-care ADL<br>4: Not applicable<br>5: Not applicable | - Questionnaire and medical record validation<br>- FSH<br>- LH<br>- Testosterone<br>- SHBG |
| Polycystic ovarian syndrome | Definition:<br>A clinical syndrome characterized by clinical or biochemical hyperandrogenism, oligo-anovulation, and polycystic ovarian morphology.[43]<br><br>Grading source:<br>St Jude modification of<br>CTCAE v4.03<br>Reproductive system and breast disorders<br>Other, specify | 1: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated (e.g., mild signs/symptoms of hyperandrogenemia)<br>2: Moderate; minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental ADL (e.g., more severe hirsutism, irregular menses; need for metformin or hormone replacement)<br>3: Severe or medically significant but not immediately life threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self-care ADL (e.g., need for surgery for cyst or bleed)<br>4: Not applicable<br>5: Not applicable | - Questionnaire and medical record validation |
| Precocious puberty | Definition:<br>A disorder characterized by unusually early development of secondary sexual features; the onset of sexual maturation begins usually before age 8 for girls and before age 9 for boys.<br><br>Grading source:<br>St Jude modification of<br>CTCAE v4.03<br>Endocrine disorders:<br>Precocious puberty | 1: Not applicable<br>2: Physical signs and biochemical markers of puberty for females <8 years and males <9 years<br>3: Not applicable<br>4: Not applicable<br>5: Not applicable | - Questionnaire and medical record validation<br>- Tanner stage<br>- Testicular volumes |

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|---|---|---|---|
| Primary ovarian failure | Definition:<br>A disorder characterized by ovarian failure before the age of 40. Symptoms include hot flashes, night sweats, mood swings and a decrease in sex drive.<br><br>Grading source:<br>CTCAE v4.03<br>Reproductive system and breast disorders: Premature menopause | 1: Not applicable<br>2: Not applicable<br>3: Present<br>4: Not applicable<br>5: Not applicable | - Questionnaire and medical record validation<br>- FSH<br>- Estradiol |
| Prostatic hypertrophy, benign | Definition:<br>A disorder characterized by compression of the urethra secondary to enlargement of the prostate gland. This results in voiding difficulties (straining to void, slow urine stream, and incomplete emptying of the bladder).<br><br>Grading source:<br>CTCAEv4.03<br>Reproductive system and breast disorders: Prostatic obstruction | 1: Diagnostic observations only; intervention not indicated<br>2: Mild symptoms; elective intervention indicated<br>3: Severe symptoms; elective operative intervention indicated<br>4: Not applicable<br>5: Not applicable | - Questionnaire and medical record validation |
| Vaginal fistula | Definition:<br>A disorder characterized by an abnormal communication between a female reproductive system organ and another organ or anatomic site.<br><br>Grading source:<br>St Jude modification of CTCAE v4.03<br>Reproductive system and breast disorders: Female genital tract fistula | 1: Asymptomatic clinical or diagnostic observations only; intervention not indicated<br>2: Symptomatic and intervention not indicated<br>3: Severe symptoms; elective operative intervention indicated<br>4: Life-threatening consequences; urgent intervention indicated<br>5: Death | - Questionnaire and medical record validation |
| Vaginal stenosis | Definition:<br>A disorder characterized by a narrowing of the vaginal canal.<br><br>Grading source:<br>St Jude modification of CTCAE v4.03<br>Reproductive system and breast disorders: Vaginal stricture | 1: Asymptomatic; mild vaginal shortening or narrowing<br>2: Vaginal narrowing and/or shortening not interfering with physical examination<br>3: Vaginal narrowing and/or shortening interfering with the use of tampons, sexual activity or physical examination (e.g., surgical intervention indicated or performed)<br>4: Not applicable<br>5: Not applicable | - Questionnaire and medical record validation |

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| NEOPLASMS | | | |
|---|---|---|---|
| **Health condition** | **Definition and Grading source** | **Grading** | - **ALL-STAR data** |
| Benign neoplasms | Definition:<br>Neoplasms benign, malignant and unspecified (incl cysts and polyps).<br>Other, specify<br><br>Grading Source<br>ST Jude Modification of CTCAE v4.03<br>Neoplasms, benign, malignant | 1: Low grade or benign neoplasms where surgical intervention is not indicated; observation or minimally invasive biopsy only (e.g. meningioma followed by MRI only or gastrointestinal polyps diagnosed and resected during colonoscopy)<br><br>2: Any low-grade or benign neoplasm requiring surgical intervention more than a minimally invasive biopsy. Excludes CNS or cardiothoracic surgical interventions (e.g. fibroadenomas, thyroid adenomas, gastrointestinal polyps requiring surgical resection)<br><br>3: Any low-grade or benign neoplasm requiring CNS or cardiothoracic surgical intervention (e.g. meningioma or myxoma requiring intervention)<br><br>4: Life-threatening consequences; urgent intervention indicated<br><br>5: Death | - Questionnaire and medical record validation |
| Malignant neoplasms | Definition:<br>Neoplasms benign, malignant and unspecified (incl cysts and polyps).<br>Other, specify<br><br>Grading Source<br>ST Jude Modification of CTCAE v4.03<br>Neoplasms, benign, malignant | 1: Asymptomatic or mild symptoms; clinical or diagnostic observations only; low-grade neoplasms where intervention is not indicated (e.g. cervical dysplasia/CIN and teratoma incidentally identified on imaging)<br><br>2: Moderate symptoms; minimal, local, or noninvasive intervention indicated; limiting age appropriate instrumental ADL; low-grade, non-metastatic neoplasms (e.g. cervical carcinoma *in situ*, cervical lymph node paraganglioma, basal cell carcinoma, squamous cell carcinoma, parotid carcinoma)<br><br>3: Severe or medically significant, but not immediately life-threatening; hospitalization indicated; disabling; limiting self-care ADL; high-grade neoplasms where single-treatment therapy required (surgery, radiation with or without chemotherapeutic agent; e.g. breast cancer if *in situ*, prostate cancer, meningioma requiring intervention, bladder carcinoma, thyroid cancer, carcinoid, squamous cell carcinoma cervix, glioma, astrocytoma, gastrointestinal stromal tumor)<br><br>4: Life-threatening consequences; urgent intervention indicated; high-grade neoplasms where multimodal therapy required or more than one chemotherapy agent used (e.g. MDS, AML, ALL, Hodgkin lymphoma, non-Hodgkin lymphoma, non-*in situ*/invasive breast cancer, osteosarcoma, Ewing sarcoma, primitive neuroectodermal tumor, soft tissue sarcoma, renal cancer, anaplastic CNS Timor, glioblastoma, carcinoma of head/neck, liver cancer, lung cancer, mesothelioma, melanoma)<br><br>5: Death | - |

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Supplementary Table 2.
Overview of the ALL-STAR questionnaire content and versions.

| **Domains** | **Items** | **Age < 15, M+F Proxy** | **Age 15-18 M+F Proxy** | **Age 15-18 M Self** | **Age 15-18 F Self** | **Age >= 18 M Self** | **Alder >=18 F Self** |
|---|---|---|---|---|---|---|---|
| Contact info | **Contact info** | x | x | x | X | x | x |
| | **Relation to subject** | x | x | | | | |
| Health care | **Leukemia follow-up** | x | x | x | x | x | X |
| | **Use of health care[1]** | x | x | x | x | x | X |
| Medicine | **Use of medicine[2]** | x | x | x | x | x | X |
| Health conditions | **Diagnoses and symptoms[3]** | x | x | x | x | x | X |
| | **Puberty[3]** | x | x | x | x | x | X |
| | **Fertility[3]** | (x) | (x) | x | x | x | X |
| | **Erectile dysfunction[3]** | | | | | X | |
| | **Surgeries** | x | x | x | x | x | X |
| | **Cancer (other than leukemia)** | x | x | x | x | x | X |
| Familiar dispositions | **Familiar dispositions** | x | x | | | x | X |
| | **Parent height and weight** | x | x | | | x | x |
| Health behavior | **Smoking** | x | x | x | x | x | X |
| | **Alcohol** | x | x | x | x | x | X |
| | **Drugs** | | | x | x | x | x |
| | **Level of physical activity** | x | x | x | x | x | X |
| | **Sedentary behavior** | x | x | x | x | x | X |
| | **Extracurricular activities** | x | x | x | x | x | X |
| | **Diet** | x | x | x | x | x | X |
| Socioeconomics | **Family structure** | x | x | x | x | x | X |
| | **Relationships/marriage/divorce** | | | x | x | x | x |
| | **Type of housing** | x | x | x | x | x | X |
| | **Educational achievements and difficulties** | x | x | x | x | x | X |
| | **Parents educational level** | x | x | x | x | x | x |
| | **Employment status** | | | x | x | x | X |
| | **Household income** | x | x | | | x | X |
| Psychosocial instruments[4] | **Health-related quality of life** | | | | | | |
| | **Fatigue** | x | x | x | x | x | X |
| | **Social relations** | x | x | x | x | x | x |
| | **Anxiety** | x | x | x | x | x | X |
| | **Depressive symptoms** | x | x | x | x | x | X |
| | **Post-traumatic stress** | x | x | x | x | x | X |
| | **Post-traumatic growth** | | | x | x | x | X |
| Cognitive[4] | **Executive function** | x | x | x | x | x | x |

1) Including active leukemia follow-up for survivors
2) Prescription- and non-prescription medicine / supplements during the preceding 12 months
3) Respondents are instructed to only answer yes to specific diagnoses if confirmed by a medical doctor. Symptoms are reported subjectively. Respondents are instructed to answer yes if the symptom/condition is present or has been present at any time point. If respondents answer yes, pop-up items require about 1) age at first occurrence, 2) multiple events where applicable, 3) if the condition/symptom is present today, and 4) how much the condition/symptom impacts on every-day life (on a 5-point Likert like scale). Survivors (not controls) are also asked whether the condition was present prior to leukemia diagnosis.
4) An overview of the standardized instruments used to evaluate emotional and cognitive function is provided in S5

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Supplementary Table 3. ALL-STAR examination program and clinical investigators.

| **Examination program** | | |
|---|---|---|
| **Time** | **Clinic** | **Activity/Investigations** |
| 7.30–8.00 am | ALL-STAR clinic | - Confirmation of consent<br>- Receipt of morning urine sample (collected at home)<br>- Measurement of height, weight and waist circumference<br>- Drawing of blood samples<br>(collection of samples for central lab) |
| 8.00–8.30 am | | *Breakfast* |
| 8.30-10.00 am | ALL-STAR clinic | - Tanner evaluation<br>- Questionnaires<br>  o Validation of ALL-STAR questionnaire completed prior to the examination day<br>  o Total Neuropathy Score (TNS) self-report items<br>  o COMPASS31 items<br>- TNS clinical tests<br>- Electrophysiological evaluation<br>- Holter record<br>- Spot urine dip stick test |
| 10.00–11.15 am | Physical test lab | - Physical performance tests<br>- Cardiorespiratory fitness bike test<br>- Dispensing of accelerometer and instructions for 7-day recording |
| 11.30–12.00 am | Department of radiology, ultrasound section | - Ultrasound scan of<br>  o Liver and gallbladder<br>  o Spleen<br>  o Pancreas<br>  o kidney |
| 12.15–12.45 pm | Department of cardiology, imaging section | - Speckle Tracking Echocardiography<br>- 12-Electrocardiogram |
| 12.45–13.30 pm | | *Lunch* |
| 13.30–13.50 | Department of Growth and reproduction | - DXA scan<br>  o Lumbar spine scan<br>  o Dual-femur bone scan<br>  o Whole body scan |
| 14.00–15.30 | Department of cardiology, imaging section | - Cardiac MRI scan |
| 15.30–16 | | *Break and snacks* |
| 16.00–17 | Department of paediatrics, Division of Pulmonology | - Spirometry<br>- Nitrogen multiple breath washout<br>- Single breath diffusion capacity |
| 17.00–17.45 | ALL-STAR clinic | - Orofacial and dental evaluation<br>- Measurement of whole saliva flow rates<br>- Collection of whole saliva samples |

Abbreviations: COMPASS31 = Composite Autonomic Symptom Score with 31 items; TNS = Total Neuropathy Score; MRI = magnetic resonance imaging

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**Clinical investigators.**

Measurement of height, weight, waist circumference, pubertal evaluation, electrocardiogram (ECG), Holter recording, physical tests, cardiopulmonary exercise test (CPET), pulmonary function tests, dual-energy X-ray absorptiometry (DXA) and neurological tests are performed by a trained and certified research team consisting of nurses and physicians at each site. Dental evaluations are performed by one dentist at one site only. Abdominal ultrasound scans are performed and evaluated by the same two ultrasound radiologists. Cardiac imaging is performed by trained echo technicians and MR radiographs at each site and images are evaluated centrally by the same team of blinded cardiologists. Standard blood tests are performed at the central laboratory at each university hospital. For tests where methodology differ at the two sites, blood samples are sent for central analysis at Copenhagen University Hospital. An advisory board consisting of physicians and senior researchers within the fields of pediatric oncology, endocrinology, physiotherapy, neurology, cardiology, pulmonology, gastroenterology, nephrology, immunology, ophthalmology, odontology, and diagnostic imaging perform continuous supervision of procedures and collected data across both study sites.

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Supplementary Table 4. Standardized questionnaire instruments.

| **Psychosocial standardized instruments included in the ALL-STAR questionnaire** | | |
|---|---|---|
| Domain | Instrument and version | ALL-STAR respondent group |
| Health-related quality of life | Pediatric Quality of Life Inventory (PedsQL)® core, version 4.0, young adults, self-report | Survivors and controls, aged > 18 |
| | PedsQL® core, version 4.0, teenagers | Survivors and controls, aged 15–18 |
| | PedsQL® core, version 4.0, teenagers, proxy-report | Parents/guardians for survivors and controls aged 15–18 |
| | PedsQL® core, version 4.0, children aged 8-12, proxy report | Parents/guardians for survivors and controls aged 8-15 |
| Fatigue | PedsQL® Fatigue, version 4.0, young adults, self-report | Survivors and controls, aged > 18 |
| | PedsQL® Fatigue, version 4.0, teenagers, self-report | Survivors and controls, aged 15–18 |
| | PedsQL® Fatigue, version 4.0, teenagers, proxy-report | Parents/guardians for survivors and controls aged 15–18 |
| | PedsQL® Fatigue, version 4.0, children aged 8-12, proxy-report | Parents/guardians for survivors and controls aged 8-15 |
| Social relations | PROMIS® Emotional support – Short Form 8a, adult, self-report | Survivors and controls, aged > 18 |
| | PROMIS® Pediatric Item bank v.1.0, Family Relationships – Short Form 8a | Survivors and controls, aged 15–18 |
| | PROMIS® Pediatric Item bank v.2.0, Peer Relationships – Short Form 8a | Survivors and controls, aged 15–18 |
| | PROMIS® Parent Proxy Item bank v.1.0, Family Relationships – Short Form 8a | Parents/guardians for survivors and controls aged <18 |
| | PROMIS® Parent Proxy Item bank v.2.0, Family Relationships – Short Form 7a | Parents/guardians for survivors and controls aged <18 |
| Anxiety | PROMIS® Item bank v. 1.0, Emotional distress – Anxiety -Short Form 8a | Survivors and controls, aged > 18 |
| | PROMIS® Pediatric Item bank v. 2.0, Emotional distress – Anxiety - Short Form 8a | Survivors and controls, aged 15–18 |
| | PROMIS® Parent Proxy Item bank v. 2.0, Emotional distress – Short Form 8a | Parents/guardians for survivors and controls aged <18 |
| Depressive symptoms | PROMIS® Item bank v. 1.0, Emotional distress – Depression -Short Form 8a | Survivors and controls, aged > 18 |
| | PROMIS® Pediatric Item bank v. 2.0, Emotional distress – Depressive Symptoms - Short Form 8a | Survivors and controls, aged 15–18 |
| | PROMIS® Parent Proxy Item bank v. 2.0, Emotional distress – Depressive Symptoms - Short Form 6a | Parents/guardians for survivors and controls aged <18 |
| Post-traumatic stress | Impact of event scale – revised® (IES-R), age > 18, self-report | Survivors, aged > 18 |
| | Child Revised Impact og Events Scale® (CRIES)-8, age 8-18, self-report | Survivors, aged 15–18 |
| | CRIES-13®, age 8-18, proxy report | Parents/guardians for survivors and controls aged 8–18 |
| Post traumatic growth | Post traumatic Growth Inventory® (PTG) | Survivors, aged > 15 |
| Executive function | Behavior Rating Inventory of Executive Function® (BRIEF)-V, ages 18-90, self-report | Survivors and controls, aged > 18 |
| | BRIEF-SR®, age 11-18, self-report | Survivors and controls, aged 15–18 |
| | BRIEF®, age 5-18, proxy-report | Parents/guardians for survivors and controls aged <18 |

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**STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology***
**Checklist for cohort, case-control, and cross-sectional studies (combined)**

| Section/Topic | Item # | Recommendation | Reported on page # |
|---|---|---|---|
| **Title and abstract** | 1 | (*a*) Indicate the study's design with a commonly used term in the title or the abstract | 3 |
| | | (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found | 3 |
| **Introduction** | | | |
| Background/rationale | 2 | Explain the scientific background and rationale for the investigation being reported | 5-6 |
| Objectives | 3 | State specific objectives, including any pre-specified hypotheses | 6+8 |
| **Methods** | | | |
| Study design | 4 | Present key elements of study design early in the paper | 6 |
| Setting | 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection | 7 |
| Participants | 6 | (*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up<br>*Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls<br>*Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants | 7 |
| | | (*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed<br>*Case-control study*—For matched studies, give matching criteria and the number of controls per case | 7 |
| Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable | 7-16 + supplementary table 1 |
| Data sources/ measurement | 8* | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group | 7-16 + supplementary table 1 |
| Bias | 9 | Describe any efforts to address potential sources of bias | 19 |
| Study size | 10 | Explain how the study size was arrived at | 17 |
| Quantitative variables | 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why | 17 |
| Statistical methods | 12 | (*a*) Describe all statistical methods, including those used to control for confounding | 17 |
| | | (*b*) Describe any methods used to examine subgroups and interactions | 17 |
| | | (*c*) Explain how missing data were addressed | NA |
| | | (*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed<br>*Case-control study*—If applicable, explain how matching of cases and controls was addressed | 17 |

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| | | | |
|---|---|---|---|
| | | *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy | |
| | | (*e*) Describe any sensitivity analyses | NA |
| **Results** | | | |
| Participants | 13* | (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed | NA |
| | | (b) Give reasons for non-participation at each stage | NA |
| | | (c) Consider use of a flow diagram | NA |
| Descriptive data | 14* | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders | NA |
| | | (b) Indicate number of participants with missing data for each variable of interest | NA |
| | | (c) *Cohort study*—Summarise follow-up time (eg, average and total amount) | NA |
| Outcome data | 15* | *Cohort study*—Report numbers of outcome events or summary measures over time | NA |
| | | *Case-control study*—Report numbers in each exposure category, or summary measures of exposure | NA |
| | | *Cross-sectional study*—Report numbers of outcome events or summary measures | NA |
| Main results | 16 | (*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included | NA |
| | | (*b*) Report category boundaries when continuous variables were categorized | NA |
| | | (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period | NA |
| Other analyses | 17 | Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses | NA |
| **Discussion** | | | |
| Key results | 18 | Summarise key results with reference to study objectives | NA |
| Limitations | 19 | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias | 19 |
| Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence | NA |
| Generalisability | 21 | Discuss the generalisability (external validity) of the study results | NA |
| **Other information** | | | |
| Funding | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based | 21 |

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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