APPENDIX

INCLUDE ONLY MALIGNANT TUMOURS

For all tumours, definition of Toronto stage is according to the guidelines published in the Lancet Oncology 2016 and 2020 by Gupta et al. [1,2] and detailed as guidelines for cancer registries by Aitken et al. [3]

Optional variables for collection are **Treatments** given as part of first line therapy (or within 1yr of diagnosis if the intended first line treatment is unclear or cannot be ascertained); data on first **relapse** or **progression,** the **cause of death** and collection of non-stage prognostic factors (**NSPs**) defined by an expert consensus process in the meeting of the Toronto group in Lyon in 2019 and published in [2] above.

Please find below specifications for each tumour type:

Medulloblastoma

We define it according to the International Classification childhood Cancer ICCC-3rd.

ICCC-3.1 diagnostic group/subgroup and ICD-O codes for morphology codes are:
3c.1 – Medulloblastomas: 9470-9472, 9474, 9480
ICD-O-3 site codes: C700-C729, C753

Cases aged up to <15 years.

	ICDO3	ICDO3.2
Medulloblastomas	9470-9472, 9474, 9480 9470:Medulloblastoma, NOS 9471:Desmoplastic nodular medulloblastoma 9472:Medullomyoblastoma 9474:Large cell medulloblastoma 9480:Cerebellar sarcoma, NOS (obsolete)	9470-9472, 9474-9477 9470:Medulloblastoma, NOS 9471:Desmoplastic nodular medulloblastoma 9472:Medullomyoblastoma 9474:Large cell medulloblastoma 9475:Medulloblastoma, WNT-activated, NOS 9476:Medulloblastoma, SHH-activated and TP53 mutant 9477:Medulloblastoma, non-WNT/non-SHH

The definition of stage by imaging has to be at the **time of diagnosis, prior to surgical resection.** The cerebro-spinal-fluid (CSF) testing needs to be by lumbar puncture and is usually recommended to be performed at day 14. Moreover, intraventricular sampling of the CSF, often done at surgery, is not used in staging. If any earlier result is negative, it does not need repeating. If an earlier result is positive, it must be repeated at or after day 14 to reduce false positives. This means that cases may need to be followed for some time after the hospital discharge, to complete staging. Furthermore, investigations performed to exclude distant metastases may be used if they occur within a short time after surgery to the primary tumour providing it is before any systemic therapy is started.

The TG (Table 1) follows the staging proposed by Harisiadis, C.H. Chang [4].

Imaging necessary for the definition of stage are computed tomography (CT) and magnetic resonance imaging (MRI) of brain and spine and whole neuraxis. To exclude metastasis, the cerebrospinal fluid (CSF) is crucial, because slightly more than 30% of children [5] have evidence of disseminated disease at presentation. Therefore, both the imaging and pathology/cytology reports include the elements needed to exclude M or to define M1,2,3,4. If multiple metastasis had been involved the worst grade should be collected. No visible disease on imaging beyond primary site of disease and no tumour cells in the cerebrospinal fluid define a localised lesion M0. The Australian paper by Aitken showed 31% and the Italian paper by Sacerdote [6] found 40% of children with metastatic medulloblastoma. However, the latter study had a higher percentage of missing stage than the Australian study. If multiple metastases are documented, assign the patients to the higher stage. If no CSF cytology result is available, then the Toronto stage cannot be assigned.

Feasibility study (optional variables):

- Collection of treatment, recurrence or relapse or progression, cause of death.
- Collection of non-stage prognostic factor (NSP).
- collection of post-surgery residual volume. (Defined as: R0= no residual cerebellar tumour; R1= residual tumour ≤1.5 cm2; R2 = residual tumour > 1.5 cm2; R+= residual tumour with unknown volume; R9=Unknown presence of residual tumour).

Non-stage prognostic factors for medulloblastoma: only molecular classification was endorsed as an additional NSP, categorised as Wingless *(WNT, 10-15% of cases)* versus Sonic Hedgehog (*SHH, 30% of cases))* vs group 3 or group 4 medulloblastomas, by the Toronto expert consensus process as an "additional" NSP [2]. This molecular classification **is also collected by the ICD-O-3.2**. WNT MB has the most favourable outcome among MB and can be regarded as 'the low-risk group'. Accordingly, studies are being designed to reduce the intensity of therapy in order to minimize long-term toxicities. The SHH MB has intermediate and poor prognosis and a bimodal age distribution.

A further prognostic factor used in clinical risk stratification is the residual tumour volume assessed by MRI immediately post-surgery. However, this was not deemed to be feasible for cancer registries to collect by the consensus process evaluating non-stage prognostic factors for the Toronto guideline process.

Table 1: Staging system for **Medulloblastoma** (Toronto guidelines)

Medulloblastoma
Tier 2 follows the M staging system

Staging criteria for medulloblastoma			
TIER 1		**TIER 2**	
Localized	Localized disease	**M0**	No visible disease on imaging (MRI brain and spine) beyond primary site of disease and no tumour cells in the cerebrospinal fluid (CSF)
Metastatic	Disease beyond local site (e.g., other lesions in brain or spine, tumour cells in CSF or distant metastases	**M1**	Tumour cells in the CSF
		M2	Visible metastasis in brain
		M3	Visible metastasis in spine or visible metastasis in cervicomedullary (junction)
		M4	Metastasis outside of the central nervous system

Osteosarcoma

We define it according to the ICCC-3rd ed. Diagnostic subgroup and morphology codes:
8a – Osteosarcoma: 9180-9187, 9192-9195 and ICD-O-3 site codes: C400-C419, C760-C768, C809.

Cases aged up to <20 years.

	ICDO3	ICDO3.2
Osteosarcoma	9180-9187, 9192-9195 9180:Osteosarcoma, NOS 9181:Chondroblastic osteosarcoma 9182:Fibroblastic osteosarcoma 9183:Telangiectatic osteosarcoma 9184:Osteosarcoma in Paget disease of bone 9185:Small cell osteosarcoma 9186:Central osteosarcoma 9187:Intraosseous well differentiated osteosarcoma 9192:Parosteal osteosarcoma 9193:Periosteal osteosarcoma 9194:High grade surface osteosarcoma 9195:Intracortical osteosarcoma	9180-9187, 9192-9195 9180:Osteosarcoma, extraskeletal 9181:Chondroblastic osteosarcoma 9182:Fibroblastic osteosarcoma 9183:Telangiectatic osteosarcoma 9184:Osteosarcoma in Paget disease of bone 9185:Small cell osteosarcoma 9186:Central osteosarcoma 9187:Low grade central osteosarcoma 9192:Parosteal osteosarcoma 9193:Periosteal osteosarcoma 9194:High grade surface osteosarcoma 9195:Intracortical osteosarcoma

The definition of stage has to be at the **time of diagnosis, prior to any treatment.** Exceptionally, investigations performed to exclude distant metastases may be used if they occur within a short time after surgery to the primary tumour providing it is before any systemic therapy is started.

Osteosarcoma affects more old children (>10 years of age), according to the Aitken study about 1 of 4 of cases present at diagnosis with distant metastasis. There is a large difference in five-year survival between localised and metastatic disease, in the Aitken et al paper this is 85% vs 37%.
Although more detailed staging systems exist, their clinical and prognostic value is limited; multi-tiered staging systems were not deemed appropriate. Only two stages are recommended (localized or metastatic) for both Tier 1 and Tier 2 (Table 2). Tumour confined to the organ or area of origin (localised), includes regional lymph nodes, while M includes distant metastatic disease.

To be noted that “skip lesions”, “skip metastases” or “seeding” in the same bone as the primary tumour are considered localized and not metastatic disease; if in a different bone to the primary tumour these are considered metastatic (Table 3)[3].
Imaging necessary for investigation of the extension of the disease are chest x-ray, CT thorax, MRI primary site, isotope bone scan and positron emission tomography (PET). Tissue biopsy is necessary for histological diagnosis.

Feasibility study (optional variable):

- Collection of treatment, recurrence or relapse or progression and cause of death.
- Non-stage prognostic factors: none recommended in Gupta et al., LO 2020 [2]

Table 2: Staging system for **Osteosarcoma** (Toronto guidelines)

Staging criteria for osteosarcoma			
TIER 1		**TIER 2**	
Localized	Tumour confined to the area of origin including regional lymph nodes	**Localized**	Tumour confined to the area of origin including regional lymph nodes
Metastatic	Distant metastases present	**Metastatic**	Distant metastases present

Definitions and notes
"skip lesions", "skip metastasis" or "seeding" in the same bone as the primary tumour are considered localized and not metastatic; if in a different bone to the primary tumour these are considered metastatic

Ewing sarcoma (of bone only)

We define it according to the ICCC-3rd ed. Diagnostic subgroup and morphology codes:
8c1 – Ewing Tumour and Askin Tumour of Bone: 9260 and ICD-O-3 site codes: C400-C419, C760-C768, C809 and 9365 in site codes C400-C419
8c2 – pPNET of Bone: 9364 and ICD-O-3 site codes: C400-C419

Cases aged up to <20 years.

	ICDO3	ICDO3.2
Ewing/Askin tumour of Bone	9260, 9365 9260:Ewing sarcoma 9365:Askin tumour	9364, 9365 9364:Ewing sarcoma 9365:Askin tumour
pPNET of Bone	9364:Peripheral neuroectodermal tumour	9364:Ewing sarcoma

Note that the code 9363 (melanotic neuroectodermal tumour) is excluded.

The definition of stage has to be at the time of diagnosis, prior to any treatment. Exceptionally, investigations performed to exclude distant metastases may be used if they occur within a short time after surgery to the primary tumour providing it is before any systemic therapy is started.

According to the updated TG [2], the staging system of Ewing sarcoma is the same of that of osteosarcoma (Table 2). Therefore, Ewing sarcoma can be combined with osteosarcoma in a single group of bone sarcomas. From the Australian paper 36% of cases are in Stage M therefore the majority is in stage L[6]. The investigations required for staging ES are CT thorax, CT/MRI primary site, Bone marrow aspirates, Bone marrow biopsy (trephine), Isotope bone scan, thorax x-ray and positron emission tomography (PET).

Feasibility study (optional variable):

- collection of treatment, recurrence or relapse or progression and cause of death.
- Non-stage prognostic factors: none recommended by Gupta et al., LO 2020 [2].

Table 3: Staging system for **Ewing sarcoma** (Toronto guidelines)

Staging criteria for Ewing sarcoma			
TIER 1		**TIER 2**	
Localized	Tumour confined to the area of origin including regional lymph nodes	**Localized**	Tumour confined to the area of origin including regional lymph nodes
Metastatic	Distant metastases present	**Metastatic**	Distant metastases present

Definitions and notes
"skip lesions", "skip metastasis" or "seeding" in the same bone as the primary tumour are considered localized and not metastatic; if in a different bone to the primary tumour these are considered metastatic

Rhabdomyosarcoma

We define it according to the ICCC-3rd ed. Diagnostic subgroup and morphology codes ICCC-3 diagnostic group/subgroup and morphology codes: 9a – Rhabdomyosarcomas: 8900-8902, 8910, 8912, 8920 and ICD-O-3 site codes:C000-C809.

Cases aged up to <20 years.

	ICDO3	ICDO3.2
Rhabdomyosarcomas	8900-8902, 8910, 8912, 8920 8900:Rhabdomyosarcoma, NOS 8901:Pleomorphic rhabdomyosarcoma, adult type 8902:Mixed type rhabdomyosarcoma 8910:Embryonal rhabdomyosarcoma 8912:Spindle cell rhabdomyosarcoma 8920:Alveolar rhabdomyosarcoma	8900-8902, 8910, 8912, 8920 8900:Rhabdomyosarcoma, NOS 8901: Pleomorphic rhabdomyosarcoma, adult type 8902:Mixed type rhabdomyosarcoma 8910:Embryonal rhabdomyosarcoma 8912:Spindle cell rhabdomyosarcoma 8920:Alveolar rhabdomyosarcoma

Note that 8991 (embryonal sarcoma) is excluded.

The definition of stage has to be at the **time of diagnosis, prior to any treatment,** according to standard clinical TNM rules with nodal involvement assessed by imaging and/or lymph node biopsy, if performed prior to chemotherapy. Exceptionally, investigations performed to exclude distant metastases may be used if they occur within a short time after surgery to the primary tumour providing it is before any systemic therapy is started.

Staging evaluation includes computed tomography (CT) of the chest, thorax x-ray, CT/MRI primary site, imaging of regional lymph nodes with positron emission tomography (PET), bone scan, bone marrow (BM) aspirate and biopsy in certain clinical scenarios.

Clinical risk stratification of rhabdomyosarcoma incorporates tumour size (more or less than 5cm), anatomical site of the primary tumour (favourable versus unfavourable), histological subtype and anatomical site of metastases, if present. Therefore, one needs to consider the site of the lesion (favourable or not), the size of the tumour (more or less than 5 cm), the regional extension, the presence of nodal metastases, and the metastatic disease. For the latter is crucial to know the site of metastases which have to be collected as well (Table 4).
Based on the Australian paper, 23% were metastatic at diagnosis and 33% in stage I [5].

In rhabdomyosarcoma, several other factors are used to determine clinical risk stratification for treatment selection: anatomical site (favourable vs unfavourable, see Table 4)) and histological subtype (embryonal vs alveolar). Thus, to report the more specific morphology code is recommended. These are routinely collected as part of registry procedures.

Feasibility study (optional variable):

- Collection of treatment, recurrence or relapse or progression and cause of death.
- Collection of NSP.

NSP for rhabdomyosarcoma: cyto-/molecular genetics, specifically the presence of FKHR-PAX3 or FKHR-PAX7 was endorsed as an “additional” by Gupta et al., [2]. This information if available in the clinical/pathologic reports should be collected as an NSP [2]

Table 4: Staging system for **Rhabdomyosarcoma** (Toronto guidelines)

Staging criteria for rhabdomyosarcoma			
TIER 1		**TIER 2**	
Localized	Tumour confined to the area of origin including the regional lymph nodes	**Stage I**	Favourable sites: orbit, head and neck (excluding parameningeal tumours) and genitourinary sites (excluding bladder and prostate tumours) and Any T Any N M0
		Stage II	Unfavourable site and T1a, T2a N0 M0
		Stage III	Unfavourable site and T1a, T2a N1 M0 T1b, T2b Any N M0
Metastatic	Distant metastases present	**Stage IV**	Any site Any T Any N M1

Table 5: Staging system for Rhabdomyosarcoma: **list of prognostic anatomic sites, tumour size, definition of N and M.**

Definitions and notes
Favourable and unfavourable anatomic sites of disease **Favourable anatomic sites:** - Orbit - Head and neck (excluding parameningeal tumours) • Scalp • Parotid • Oral cavity • Larynx • Oropharynx • Cheek • Hypopharynx • Thyroid and parathyroid • Neck - Genitourinary sites (excluding bladder and prostate tumours) - Gallbladder and bile ducts **Unfavourable anatomic sites:** - Bladder - Prostate - Extremity - Parameningeal • Middle ear • Nasal cavity • Paranasal sinuses • Nasopharynx • Infratemporal fossa/pterygopalatine • Parapharyngeal area - Trunk - Retroperitoneum - All other sites not noted as favourable **T - Tumour size** T0 = no evidence of primary tumour T1 = tumour confined to a single anatomic site T1a = tumour ≤ 5cm in greatest dimension T1b = tumour > 5cm in greatest dimension T2 = extension beyond anatomic site T2a = tumour ≤ 5cm in greatest dimension T2b = tumour > 5cm in greatest dimension **Tx =** Primary tumour cannot be assessed **N - Regional nodes** N0 = regional lymph nodes not involved N1 = regional lymph nodes involved Nx = regional lymph nodes cannot be assessed (especially sites that preclude lymph node evaluation) **M - Metastasis** M0 = no distant metastasis M1 = distant metastasis

Neuroblastoma

We define neuroblastoma according to the ICCC-3rd ed.: 4a – Neuroblastoma and Ganglioneuroblastoma; ICD-O codes for morphology are 9490 and 9500 and codes for topography are C00.0-C69.9, C73.9-C76.8, C80-9.

Cases aged up to <15 years.

	ICDO3	ICDO3.2
Neuroblastoma and ganglioneuroblastoma	9490, 9500 9490:Ganglioneuroblastoma 9500:Neuroblastoma, NOS	9490, 9500 9490:Ganglioneuroblastoma 9500: Neuroblastoma, NOS

The International Neuroblastoma Risk Group Staging System should be used for both Tiers [7] (Table 5)
The INRGSS recognises that resectability partly suggests extent of disease but is also defined by the location and invasion of the tumour. These features, such as aorta encasement or tracheal compression, can be established by preoperative imaging (image-defined risk factors) (Table 6).

The definition of stage has to be at the time of diagnosis, prior to any surgical resection. Exceptionally, investigations performed to exclude distant metastases may be used if they occur within a short time after surgery to the primary tumour providing it is before any systemic therapy is started.

Imaging necessary for the definition of stage are CT/MRI primary site, abdominal ultrasound, bone scan, meta-iodobenzylguanidine (MIBG) scan, thorax x-ray and tissue biopsy, therefore information for staging are included in the reports of imaging. They are crucial to assess the invasion of vital structures.

The list of vital structures is in the appendix. Bone marrow aspirates and biopsies have to be performed to evaluate whether a marrow infiltration is present or not. See Table 4 for the staging of neuroblastoma by the TG which follows those of the INRGSS group [7].

Four risk strata are recognised: stage L1, stage L2, stage M and stage MS. Briefly, L1 and L2 differ for the invasion of vital structures. Metastases are divided into two strata based on age and on involvement of specific organs (see Table 5). MS disease refers to children < 18 months with metastases confined to skin, liver, or bone marrow. Children aged < 18 month with metastases in other sites are staged as M.

According to the Australian study, neuroblastoma present the highest % of children with metastatic disease at diagnosis (51%) and less in the JARC pilot study (38%) [5].

Feasibility study (optional variable):
Collection of treatment, recurrence or relapse or progression, cause of death and non-stage prognostic factor .
NSP for Neuroblastoma: N-myc gene amplification is supported to be collected as NSP [2,8]. It is a significant genetic marker of poor prognosis, therefore is critical for choice of therapeutic options.

Table 6: Staging system for **Neuroblastoma** (Toronto guidelines)

Staging criteria for neuroblastoma			
TIER 1		**TIER 2**	
Localized	Localized tumour not involving vital structures and confined to one body compartment	**Stage L1**	Localized tumour that does not involve any viral structures as defined by the list of IDRFs (i.e., there are no IDRFs) and the tumour must be confined within one body compartment, neck, chest, abdomen, or pelvis. An intraspinal tumour extension that does not fulfil the criteria for an IDRF is consistent with stage L1.
Locoregional	Locoregional tumour with spread	**Stage L2**	Locoregional tumour with one or more IDRFs. The tumour may be ipsilaterally contiguous within body compartments (i.e., a left sided abdominal tumour with left-sided lung, bone or pleura involvement should be considered stage L2). However, a clearly left sided abdominal tumour with right-sided lung, bone or pleura (or vice versa) involvement is defined as metastatic disease.
Metastatic	Distant metastatic disease (except stage MS)	**Stage M**	Distant metastatic disease (i.e., not contiguous with the primary tumour) except as defined for stage MS. Nonregional (distant) lymph node involvement is metastatic disease. However, an upper abdominal tumour with enlarged lower mediastinal nodes or a pelvic tumour with inguinal lymph node involvement is considered locoregional disease. Ascites and/or pleural effusion, even with malignant cells, do not constitute metastatic disease unless they are remote from the body compartment of the primary tumour.
MS	Metastatic disease confined to skin, liver, and/or bone marrow in a patient less than 18 months (547 days)	**Stage MS**	Metastatic disease confined to skin, liver, and/or bone marrow in a patient less than 18 months (547 days) MIBG scintigraphy must be negative in bone and bone marrow.

Note: Tier 1 criteria are simplified proxies of Tier 2 that do not require assessment of image-defined risk factors for use in settings where cross-sectional imaging is not available.

Table 7: Staging system for **Neuroblastoma: notes and list of the prognostic site of extension**.

Definitions and notes
Patients with multifocal primary tumours should be staged according to the greatest extent of disease as defined in the IDRF table. <u>Image-defined risk factors</u> Staging requires assessment of whether or not patients have none (stage L1) or one or more (stage L2) of the image-defined risk factors (IDRF) listed below. These are identified in reports of imaging at diagnosis, prior to any surgical resection. *- Ipsilateral tumour extension within two body compartments* Neck-chest, chest-abdomen, abdomen-pelvis *- Neck* Tumour encasing carotid and/or vertebral artery and/or internal jugular vein Tumour extending to base of skull Tumour compressing the trachea *- Cervico-thoracic junction* Tumour encasing brachial plexus roots Tumour encasing subclavian vessels and/or vertebral and/or carotid artery Tumour compressing the trachea *- Thorax* Tumour encasing the aorta and/or major branches Tumour compressing the trachea and/or principal bronchi Lower mediastinal tumour, infiltrating the costo-vertebral junction between T9 and T12 *- Thoraco-abdominal* Tumour encasing the aorta and/or vena cava *- Abdomen/pelvis* Tumour infiltrating the porta hepatis and/or the hepatoduodenal ligament Tumour encasing branches of the superior mesenteric artery at the mesenteric root Tumour encasing the origin of coeliac axis, and/or of the superior mesenteric artery Tumour invading one or both renal pedicles Tumour encasing the aorta and/or vena cava Tumour encasing the iliac vessels Pelvic tumour crossing the sciatic notch *- Intraspinal tumour extension whatever the location provided that:* More than one third of the spinal canal in the axial plane is invaded and/or the perimedullary leptomeningeal spaces are not visible and/or the spinal cord signal is abnormal *- Infiltration of adjacent organs/structures* Pericardium, diaphragm, kidney, liver, duodeno-pancreatic block, and mesentery

Wilms tumour

We define Wilms tumour according to the ICCC-3rd ed. Diagnostic subgroup and morphology codes: nephroblastoma 6a1 : ICD-O morphology codes are 8959, 8960 and topography code is C649.

Cases aged up to <15 years.

	ICDO3	ICDO3.2
Nephroblastoma	8959, 8960 8959:Malignant cystic nephroma 8960:Nephroblastoma, NOS	8959, 8960 8959:Malignant cystic nephroma 8960:Nephroblastoma, NOS

In Wilms tumour, abdominal tumour **stage is based on the surgery specimen**, whatever its timing, whereas the overall stage (localised, metastatic, bilateral) is based on imaging at diagnosis (Table 7). Two major protocols exist that generate two different staging systems. If the child was treated with the Children's Oncology Group/National Wilms Tumour Study Group (COG) protocol the staging system is based on the surgical specimen (nephrectomy) assessed prior to any chemotherapy which is only given after surgery; if the child is treated with the International Society of Paediatric Oncology (SIOP) protocol, the stage is based on the findings at surgery after the patient has received neo-adjuvant chemotherapy. Both groups recognise the presence of metastatic (stage IV) disease at diagnosis, based on imaging findings. As an individual child can only be treated by one approach, only the relevant type of stage should be filled in. (pre-fix y for the localised tumour stage if assigned after neo-adjuvant pre-operative chemotherapy).

The major imaging modalities used to assess tumour stage are abdominal ultrasound examination, cross-sectional computed tomography (CT) or magnetic resonance imaging (MRI) scans of the abdomen, CT scan thorax and/or chest radiograph and tissue biopsy. Diagnostic imaging studies play a central role in the evaluation of initial extent of disease and for planning surgery or monitoring the response to therapy. Parameters that should be carefully evaluated are the extent of the tumour within and behind the kidney, involvement of the contralateral kidney, the presence of intravascular tumour thrombosis (renal and cava veins), and the presence of retroperitoneal lymph nodes (Table 6). However, the final abdominal tumour stage is only fully determined by pathological examination of the surgical specimen after nephrectomy, and includes information provided by the surgeon (e.g., if the tumour was seen to have ruptured either before or during surgery). Regional lymph nodes should be sampled and examined histologically. Distant metastases (stage IV) in Wilms tumour are most often to the lungs, less frequently to the liver. Bone marrow assessment is not required routinely. Nodal involvement beyond the abdomen is classified as distant metastasis. The presence/absence of metastases should be evaluated at presentation, on the basis of imaging studies. Laterality and sites of metastases have to be reported. In cases of bilateral disease, stage of the most advanced kidney should be recorded. At diagnosis, if diagnostic imaging reports on the status of liver, bone brain and other sites mentions the words "suspicious", "highly suspicious", "possible" or "highly suspected", assume metastatic disease regardless of upfront surgery or chemotherapy.
The TG incorporates both systems; "y" designates SIOP stage (for patients who have received neo-adjuvant chemotherapy). It is noted that giving chemotherapy before surgery will shrink the tumour and will likely "downstage" the patient.

Children with metastatic disease, as reported by the Australian study, was 17% versus 13% of the JARC pilot study [5]. The majority of children with Wilms tumour present at diagnosis in localised stage.

Feasibility study (optional variable):

Collection of treatment, recurrence or relapse or progression, cause of death and NSP.

Non-stage prognostic factor for Wilms tumour: histological subtype. This varies according to initial treatment approach. Presence or absence of diffuse or focal anaplasia is relevant for both approaches. The high risk 'blastemal-type' WT can only be recognised if pre-operative chemotherapy has been used [9,2].

Table 8: Staging system for **Wilms tumour according to the protocol** (a) COG (b) SIOP.

a

Staging criteria for Wilms tumour based on findings at surgery for patients who <u>have not</u> received chemotherapy prior to surgery (Children's Oncology Group (COG) protocol)			
TIER 1		**TIER 2**	
Localized	Tumour confined to area of origin	**Stage I**	Tumour is limited to the kidney and completely excised: • Renal capsule intact, not penetrated by tumour • No tumour invasion of veins or lymphatics of renal sinus • No nodal or haematogenous metastases • No prior biopsy • Negative margins
		Stage II	Tumour extends beyond kidney but completely resected: • Tumour penetrated renal capsule • Tumour in lymphatics or veins of renal sinus • Tumour in renal vein with margin not involved • No nodal or haematogenous metastases • Negative margins
		Stage III	Residual tumour or non-haematogenous metastases confined to abdomen: • Involved abdominal nodes • Peritoneal contamination or tumour implant • Tumour spillage of any degree occurring before or during surgery • Gross residual tumour in abdomen • Biopsy of tumour (including free-needle aspiration) prior to removal of kidney • Resection margins involved by tumour
Metastatic	Distant metastases present at diagnosis	**Stage IV**	Haematogenous metastases or spread beyond abdomen <u>at diagnosis</u>

b

Staging criteria for Wilms tumour based on findings at surgery for patients who <u>have</u> received chemotherapy prior to surgery (International Society of Paediatric Oncology (SIOP) protocol)			
TIER 1		**TIER 2**	
Localized	Tumour confined to area of origin	**Stage y-I**	Tumour limited to kidney and completely resected: • Renal capsule may be infiltrated by tumour, but tumour does not reach the outer surface • Tumour may protrude or bulge into the pelvic system or ureter, but does not infiltrate • Vessels of renal sinus not involved
		Stage y-II	Tumour extends beyond kidney but completely resected: • Tumour penetrates renal capsule into perirenal fat • Tumour infiltrates the renal sinus and/or invades blood and lymphatic vessels outside renal parenchyma but is completely resected • Tumour infiltrates adjacent organs or vena cava but is completely resected
		Stage y-III	Incomplete excision of the tumour (gross or microscopic extension beyond the resection margins): • Involved abdominal lymph nodes, including necrotic tumour or chemotherapy-induced changes • Tumour rupture before or intraoperatively • Tumour has penetrated the peritoneal surface • Tumour thrombi present at resection margins • Surgical biopsy prior to resection (does not include needle biopsy)
Metastatic	Distant metastases present at diagnosis	**Stage IV**	Haematogenous metastases or spread beyond abdomen <u>at diagnosis</u>

References

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List of the procedures for security measures (both technical and organizational)

National Cancer Institute of Milano (INT)

Technical and organisational measures

Authentication;
Authorization;
Data encryption (ensured by Microsoft SharePoint);
Penetration test (General technical security measure aimed at protecting the system from cybercrime attacks);
Business continuity and disaster recovery (General technical safety measure aimed at protecting against technological failures or other emergencies (e.g., floods, fires));
Firewall;
Antivirus;
Intrusion detection;
Server back-up;
Adequate configuration of IT tools (e.g., password protected files; mandatory change of the password every 3 months; setting of complex password).

General organisational measures

Formal appointment of Data Protection Officer (DPO) General Director's determination n° 131/ 2017; Formal appointment of Controller's Delegates: General Director's determination n° 79/2019;
The TEAM supporting the DPO includes legal, IT and process skills;
Privacy by Design (e.g., Process only the personal data necessary for each specific purpose of the processing);
Data Protection Agreement or contractual clause from INT format or supplier format;
Formal appointment of the CSR (Information Security Manager);
Creation of courses for the entire staff (GDPR, Italian privacy legislation);
Mandatory foundation course for whole personnel updated every year;
Employment contracts include compliance with organisational information governance standards.
Secure physical access;
Personnel are authorized by the Controller and receive instructions, general and specific, about data processing (e.g., how to process data, what security measures to take, what is forbidden to do);
Destruction or anonymization of data at the end of the retention times.

Privacy policies

To promote transparency and awareness regarding data processing on the INT website there is a special section dedicated to privacy, where the main privacy policies are published.
https://www.istitutotumori.mi.it/privacy (in Italian)

UCL RESEARCH ETHICS COMMITTEE
OFFICE FOR THE VICE PROVOST RESEARCH

22nd April 2021

Professor Kathy Pritchard-Jones
GOS Institute of Child Health
Developmental Biology and Cancer Research and Teaching Dept
UCL

Dear Professor Pritchard-Jones

Notification of Ethics Approval with Provisos
Project ID/Title: 19963/001: "BENCHISTA": International Benchmarking of Childhood Cancer Survival by stage

Further to your satisfactory responses to the Committee's comments, I am pleased to confirm in my capacity as Chair of the UCL Research Ethics Committee (REC) that your study has been ethically approved by the UCL REC until 30th June 2024.

Approval is granted conditional on the research collaborators obtaining their ethics approvals and data sharing agreements between UCL and the UK registries being approved and signed.

Ethical approval is also subject to the following conditions:

Notification of Amendments to the Research
You must seek Chair's approval for proposed amendments (to include extensions to the duration of the project) to the research for which this approval has been given. Each research project is reviewed separately and if there are significant changes to the research protocol you should seek confirmation of continued ethical approval by completing an 'Amendment Approval Request Form'
http://ethics.grad.ucl.ac.uk/responsibilities.php

Adverse Event Reporting – Serious and Non-Serious
It is your responsibility to report to the Committee any unanticipated problems or adverse events involving risks to participants or others. The Ethics Committee should be notified of all serious adverse events via the Ethics Committee Administrator (ethics@ucl.ac.uk) immediately the incident occurs. Where the adverse incident is unexpected and serious, the Joint Chairs will decide whether the study should be terminated pending the opinion of an independent expert. For non-serious adverse events the Joint Chairs of the Ethics Committee should again be notified via the Ethics Committee Administrator within ten days of the incident occurring and provide a full written report that should include any amendments to the participant information sheet and study protocol.

The Joint Chairs will confirm that the incident is non-serious and report to the Committee at the next meeting. The final view of the Committee will be communicated to you.

Office of the Vice Provost Research, 2 Taviton Street
University College London
Tel: +44 (0)20 7679 8717
Email: ethics@ucl.ac.uk
http://ethics.grad.ucl.ac.uk/

Final Report
At the end of the data collection element of your research we ask that you submit a very brief report (1-2 paragraphs will suffice) which includes in particular issues relating to the ethical implications of the research i.e. issues obtaining consent, participants withdrawing from the research, confidentiality, protection of participants from physical and mental harm etc.

In addition, please:

- ensure that you follow all relevant guidance as laid out in UCL's Code of Conduct for Research: https://www.ucl.ac.uk/srs/file/579
- note that you are required to adhere to all research data/records management and storage procedures agreed as part of your application. This will be expected even after completion of the study.

With best wishes for the research.

Yours sincerely

Professor Lynn Ang
Joint Chair, UCL Research Ethics Committee

Sistema Socio Sanitario
Fondazione IRCCS Istituto Nazionale dei Tumori
Regione Lombardia

COMITATO ETICO E-mail: – Tel.: +39 02 2390 2546, 2744, 3452 – Fax: +39 02 2390 3453

Dott.ssa Gatta Gemma
Ricercatore responsabile
Sede

DI - 4622359 - 27/05/2021
Fondazione IRCCS Istituto Nazionale Tumori - Milano
SR: DSCCE

Milano, 27 Maggio 2021

Oggetto: Progetto dal titolo "Confronto internazionale della sopravvivenza per cancro in età infantile, secondo lo stadio alla diagnosi"

Promotore: University College London

In riferimento al progetto in oggetto, si comunica che durante la seduta organizzata in teleconferenza il 25 Maggio 2021, il Comitato Etico della Fondazione IRCCS "Istituto Nazionale dei Tumori" ha preso visione della documentazione presentata e informa che, per quanto di sua competenza, nulla osta all' effettuazione del progetto.

Su delega del Presidente
Dott. Giovanni Apolone

Allegati: Pagina presenze componenti CE

Sistema Socio Sanitario

Fondazione IRCCS Istituto Nazionale dei Tumori

Regione Lombardia

Il Comitato Etico della Fondazione IRCCS "Istituto Nazionale dei Tumori" la cui composizione risponde ai requisiti minimi individuati dai D.M. 08/02/13 e D.M. 12/05/06, è stato deliberato, per il triennio 01.01.2017-31.12.2019 dal CdA della Fondazione il 22.12.2016 , aggiornato il 02.04.2019 e prorogato da RL al 31/12/2021 (nota del DGW 19/04/2021)

Allegato: pagina presenze componenti CE

Riunione in teleconferenza del Comitato Etico del 25 Maggio 2021

	ASSENTE PRESENTE (A/P)
Dott. LABIANCA ROBERTO (Clinico) **Presidente**	**P**
Dott. ssa ANDREASSI AIDA (Direttore Sanitario)	**P**
Dott. APOLONE GIOVANNI (Direttore Scientifico)	**A**
In attesa di nomina (Rappresentante Professioni Sanitarie)	-
Dott. BOMBARDIERI EMILIO (Clinico)	**P**
Dott. CELENTANO CARLO (Medicina Generale Territoriale)	**P**
Dott. CEREDA EMANUELE (Esperto in Nutrizione) in relazione allo studio di prodotti alimentari sull'uomo	**P**
Dott.ssa CRIPPA FLORIANI FRANCESCA (Esperto in assistenza sanitaria)	**P**
Dott. D'INCALCI MAURIZIO (Farmacologo) **Vice Presidente**	**P**
Prof. FOA PAOLO (Clinico)	**P**
Dott. JANKOVIC MOMCILO (Pediatra)	**P**
Dott. LADISA VITO (Farmacista del SSR)	**P**
Avv. MANTOVANI RENATO (Esperto in materia giuridica)	**P**
Dott. MIADONNA ANTONIO (Clinico)	**P**
Avv. MIGONE de AMICIS AGOSTINO (Esperto in materia giuridica)	**P**
Prof.ssa MIOZZO MONICA ROSA (Esperto in genetica)	**P**
Ing. PAVESI ROBERTA ELENA (Esperto in dispositivi medici) in relazione all'area medico-chirurgica oggetto dell'indagine con il dispositivo medico in studio	**A**
Don TULLIO PROSERPIO (Esperto di bioetica)	**P**
Dott. RAMPOLDI ANTONIO GAETANO (Esperto nuove procedure) in relazione a nuove procedure tecniche, diagnostiche e terapeutiche, invasive e mini-invasive	**A**
Prof. SCAGLIONE FRANCESCO (Farmacologo)	**P**
Prof.ssa SCORSETTI MARTA (Clinico)	**P**
Dott. TORRI VALTER (Biostatistico)	**A**
Dott.ssa VETERE RITA (Volontariato/Associazionismo)	**P**

20133 Milano - via Venezian, 1 - tel. 02.2390.1 - codice fiscale 80018230153 - partita I.v.a. 04376350155

English translation of the ethical approval granted to the BENCHISTA project by the Ethical Committee of the Fondazione IRCCS, National Cancer Institute:

To Gemma Gatta
Responsible researcher of the project

Milan,

2021-05-28

Object: title of the project "International benchmarking of childhood cancer survival by stage"
Sponsor: University College London

Regarding the project in question, we inform that during the session organized by teleconference on May, 25 ,2021, the Ethical Committee of the Fondazione IRCCS "Istituto Nazionale dei Tumori" have considered the presented documentation and informs that, to the extent of its competence, there is no impediment to carrying out the project.

As delegated by the President

(signature)

Dott Giovanni Apolone

List of the committee members