Project: BENCHISTA

International benchmarking of population-based childhood cancer survival by stage at diagnosis

BENCHISTA (International Benchmarking of Childhood Cancer Survival by Stage)

BENCHISTA Study Protocol: 22nd Sep 2022, Version 4.4

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BENCHISTA protocol changes from previous versions 3.0, 4.0,4.2 and 4.3

(Revised after Project Working Group meetings 16.06.2021, 22.09.2021, 06.07.2022, Project Management Team meetings 07.06.2021, 08.09.2021, 04.07.2022 and Independent Advisory Board meeting 28.03.2022)

- Chapter 2.3.1: Inclusion of the sentence: "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."
- Chapter 2.4.1: Inclusion of the sentence "CRs should use all available sources of hospital data and enlist input from appropriate clinical staff where required to ensure consistent clinical interpretation of diagnostic investigations"
- Chapter 2.4.2: Inclusion of the sentence "The request to CRs is to report only the treatments included in the patient's planned first line therapy. If a registry is not able to identify what is first line therapy, we recommend including all treatments given in the first 12 months following the date of diagnosis."
- Chapter 2.5: inclusion of the sentence "There are a few exceptions among the CRs (Finland, Japan and Poland) and new checks will be carried out to ensure the coverage of these specific registries."
- Chapter 4: Description of the UCL and INT ethical approvals and inclusion of their approvals in the appendix. Rules for the transfer agreement between CRs and INT for the database transmission and mail address for communication between CRs and INT. Inclusion of the sentences: " UCL and INT will act as joint Data Controllers for the project, with responsibilities as defined by article 26, GDPR", "The BENCHISTA project working group includes representation from all PBCRs contributing data to the project, as well as tumour-specific clinical leads from the relevant European clinical trials groups, parent and patient representation and the principal investigators at University College London and INT, Milan." and "The BENCHISTA data remain the property of the contributing registries, whose consent is required before they can be used for purposes other than those originally envisaged in the BENCHISTA protocols. All members of the Working Group that provide data must be informed of any analysis being carried out."
- Chapter 6: list of the PMT and IAB members
- Chapter 7: modification of the data providers list
- Use of clinical TNM (cTNM) only for TG Rhabdomyosarcoma tier 2 staging.
- Table 2: Addition of the variables about each exam's result
- Table 2: Removal of variables about clinical staging documentation and its discrepancy with TG staging
- Table 2: Definition of the residual volume variable for Medulloblastoma as optional
- Table 2: Addition of the modality 3='Both preoperative and postoperative chemo" and 4='Chemotherapy only' in the 'Chemotherapy type' variable
- Table 2: Addition of three variables for a possible second previous cancer: 'second previous cancer', 'second previous cancer definition' and 'year of diagnosis of the second previous cancer'
- Table 2: Removal of the variable: 'CT/MRI primary site outcome'
- Change in the meaning of the variable about the examinations/imaging. The meaning has been changed from "examination/imaging used *by the registrar* for obtaining the Toronto stage" to "examination/imaging performed ", even if not used directly by the registrar to construct the Toronto stage. The values and modalities of the variables have not been changed

Amendment N.1 (Protocol version 4.2 to version 4.3) – approved 08 Feb 2022

- UCL and INT will act as joint Data Controllers for the project. Only INT has access to pseudo anonymised personal data and UCL does not. No individual patient-level data will be sent to UCL.

Data flows between individual cancer registries and the INT, Milan, according to project-specific data sharing agreements signed directly between the CR and the INT.

- Chapter 4: The project database will be retained at INT (data controller) for 10 years and then will be securely deleted (prolonged from 5yrs at the request of the participating cancer registries, to ensure sufficient time for all possible analyses and post-publication queries to be answered).

Amendment N. 2 (Protocol version 4.3 to version 4.4)

- Change of wording from Data Sharing Agreement (DSA) to Data Transfer Agreement (DTA).
- Chapter 2.6: Extension for data submission to November 2022.
- Chapter 4: Change in data transfer system from *WeTransfer* to *Microsoft SharePoint*. Change approved by the INT's IT department and agreed with the cancer registries requiring it for this project (some cancer registries transfer the data through their own systems).
- Funder's approval for a 7-month project funding no-cost extension (new end date 31st Jan 2024).
- Chapter 7: Change of the chapter's name for clarity (from *Data providers* to *Participating registries*) and inclusion of updates (NDRS transferred from PHE to NHS Digital and mention of three more Italian cancer registries previously invited to participate in the project).

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Table and Figures

1. Background and aim of the study

Population-based survival studies on childhood cancers (CC) have shown significant geographical disparities and progress during the studied time periods, both within and outside Europe [1,2]. Both time and space outcome differences can be explained by changes in tumour stage at presentation. We know that cancer is diagnosed at a somewhat more advanced stage in the UK compared to several Western European countries and this may be sufficient to explain the small but statistically significant survival differences seen in international comparisons within the same multi-national clinical trial [3]. Additional factors that may explain survival differences between countries are differences in diagnostic accuracy and in treatment [4].

Most population-based cancer registries (PBCRs) hold incomplete data on tumour stage for childhood cancers. This is because staging systems used for adult cancers are not easily applicable to childhood cancer and access to necessary clinical data sources to assign tumour stage is difficult. In 2014, an international working group developed consensus staging guidelines for paediatric cancers, known as the "Toronto" guidelines (TG) [5]. The feasibility of PBCRs applying these guidelines was tested in a pilot study conducted through the European Joint Action on Rare Cancers (JARC)[6,7]. The pilot project was very successful, with a high participation of PBCRs from 14 European countries. It demonstrated the current capabilities and resources required by PBCRs to acquire relevant tumour staging data from clinical registries, treating hospitals or routine health care data sources. For the two solid tumours chosen for the pilot –neuroblastoma and Wilms tumour – tumour stage could be documented for 97% of cases in a recent time period. Several PBCRs were also able to provide data on treatment and relapse.

Application of this standardised way to collect stage and a complete collection of stage at diagnosis on all cases by cancer registries is necessary for comparison and interpretation of any outcome differences in population-based analyses. It should be emphasised that Toronto staging is not used as a clinical instrument for choosing a treatment – this is done using risk stratification criteria defined by the treatment protocol applied to an individual patient and which may vary between countries and treatment centres. The importance of the Toronto staging is as a tool for cancer registries to have comparable stage information at a population-level for each of the commonly recognised childhood cancers.

The broad aims of this project are to improve understanding of the reasons for variation in childhood cancer survival between countries and to highlight areas to be targeted for improvement. Tumour stage is a determinant of the likelihood of cure and the intensity of treatment required by the cancer patient. We aim to stimulate the application of the TG by the greatest number of European PBCRs, for the most common solid paediatric cancers. The collection should be in a routine way, that is stage should be included as a mandatory variable. To do this and for conducting in a sustainable way future outcomes research, closer working relationships between PBCRs, clinical services and tumour-specific clinical study groups should be stimulated.

The specific hypotheses to be tested are:

1: Are childhood cancers diagnosed at a more advanced stage in some countries compared to others?
2: Do survival rates by tumour stage vary between countries/large geographic regions?

Hypothesis 1 assesses if evidence exists for late diagnosis of cancer in children in some countries. If significant differences are found in the proportion of children diagnosed with more advanced stage tumours, this may be

due to differences in awareness of childhood cancer signs and symptoms (by parents/public and community healthcare workers), or to differences in child health systems for routine surveillance and primary care, or to delays after referral to secondary care. All are potential targets for future interventions.

Hypothesis 2 assesses if evidence exists for variation in survival rates for the same tumour type and stage between countries/regions. If differences are found, this may be due to differences in diagnostic and treatment practices, tumour biology or supportive care. The project will test how well PBCRs can collect data on these items and relapse, so that these further hypotheses can be tested.

These questions will be addressed through the following activities:

1. Participating PBCRs will assign tumour stage at diagnosis at a population level for six specified childhood solid tumours, using the "Toronto" staging guidelines [5,8,9].
2. Participating PBCRs will share a pseudonymised patient-level dataset with the central data analysis team in Milan, including additional variables (feasibility study) where available (non-stage prognosticators, summary of primary treatment, any relapse and cause of death).
3. Comparative analysis of distribution of tumour stage at diagnosis at a population level.
4. Analysis of overall survival by stage for each tumour type, with comparisons between sufficiently large population groups (country-level or European region) for statistically powered analysis of variation and avoidance of reidentification of included cases.
5. Production of practical recommendations on strengthening joint working between PBCRs and clinical/hospital registries so that staging of newly diagnosed childhood cancer patients becomes more efficient and complete. This will allow the analysis of survival by stage to be performed in a sustainable way using routine health care data for prospective clinical observational studies in the future.

The cooperation of PBCRs with clinical/hospital data bases will also assess how easily PBCRs can collect data on first line treatment, tumour biology, non-stage prognosticators (NSP) [9] relapse and cause of death. This feasibility aspect of the project will evaluate how well PBCRs can collect these variables. This information will form the basis for development of future studies that would utilise these data items to explore in more depth the underlying reasons for any variation in survival rates. Collection of these variables will also stimulate collaboration between clinicians in charge of clinical/hospital data bases and registries and their corresponding national/regional population-based cancer registries.

We will also undertake a descriptive comparative analysis of child health practices in the countries of the participating registries. This will cover both routine child health surveillance appointments (frequency and type of practitioner) as well as usual routes to medical attention for symptomatic children. This information will add an extra dimension to understanding variation in 'routes to diagnosis' that may explain any observed differences in stage distribution at diagnosis. This information will be compiled from information already in the public domain and discussions with paediatricians and clinicians involved in the project from each participating country.

2. Methodology

2.1 Selection of tumour types

The project will study stage distribution and survival for 6 paediatric solid cancers: **medulloblastoma, osteosarcoma, Ewing sarcoma, rhabdomyosarcoma, neuroblastoma, Wilms tumour.**
These tumours have been selected based on one or more of the following considerations:

1. Generally good prognosis (Wilms tumour, localised neuroblastoma) and curability using 'standard of care' treatment regimens.
2. The important differences in outcomes already demonstrated between some populations for some tumour types.
3. Low or no improvement in survival rates over a long time period.

Together, they represent a considerable percentage (~40%) of all childhood solid tumours. The expected number of cases estimated by country for the three-year inclusion period for this study is shown in Table 1. The numbers of cases are estimated mostly from data held by the EUROCARE-6 project (2005-2013) [10].

2.2 Inclusion criteria

The updated ENCR (European Network of Cancer Registries) recommendations (https://encr.eu/sites/default/files/pdf/incideng.pdf) should be followed to record the date of incidence used by the registry to define their cases meeting the inclusion criteria.

- Cases to be included are all children aged <15yrs with the relevant histology codes (detailed in the Appendix that describes the Toronto staging systems for each tumour type). For the three cancer types that are common in adolescents (osteosarcoma, Ewing sarcoma and rhabdomyosarcoma), cases aged 15 -19 (inclusive, i.e., < 20) years of age will be included if data are held by the registry.
- Cases must be diagnosed between 01.01.2014 – 31.12.2017, one year incidence back and forth will be considered in order for a registry to have a minimum of three consecutive years' worth of cases, providing 3 years follow-up is assured.
- All consecutive incident cases must be identified and submitted by each PBCRs.
- Cases should have at least 3 years of follow-up for the definition of the life status, according to PBCR practice.
- After an agreement with the INT team, follow up data could be submitted separately and at a later timepoint during the second year of the project, to allow for maximum follow-up on all patients.

Cases with problems in the definition of stage because of scarcity of information must be included and not eliminated.

2.3 Staging process

Participating PBCRs will assign tumour stage at diagnosis using the Toronto Guidelines (TG) supported by the detailed guidance based on the Australian experience being produced as a study document [8] and translated in French, Spanish, Portuguese and Italian. The TG includes a two-tiered system to define stage [5,8]: Tier 2 staging system is more detailed and intended for use in high resource settings. The full details of Tier 1 and Tier

2 staging criteria for each tumour type are available elsewhere [8]. All PBCRs are asked to provide Tier 2 stage if they can access the clinical details, otherwise Tier 1 will be acceptable for the primary endpoints of only assessing the proportions of localised vs metastatic tumour at diagnosis. Registries will provide pseudo-anonymised descriptive information at an individual patient level. It is also asked to collect information regarding the clinical data sources for staging and the examinations performed (e.g., CT scan of chest versus Chest X-ray).
To assure registry standardisation, a two-step process is proposed. First, a training session to introduce TG and second, the creation of a quality assurance set of fictitious cases to analyse how well standardised the application of the TG is between registries.

2.3.1 General rules of staging

Toronto stage is defined as extent of disease at the time of diagnosis and is based on evidence acquired before treatment. The only exceptions are:

- Staging of localised (non-metastatic) Wilms tumour resected after pre-operative (neo-adjuvant) chemotherapy, where stage is based on surgical and pathological assessment of the nephrectomy specimen and indicated by the prefix 'y'.
- Investigations performed to exclude distant metastases might be used if they occur within a short time after surgery to the primary tumour, providing it is before any systemic therapy is started.

For rhabdomyosarcoma, tumour stage should always be defined at diagnosis according to standard clinical TNM rules with nodal involvement assessed by imaging and/or lymph node biopsy, if performed prior to chemotherapy.

For all diagnostic groups including Wilms tumour, the presence of distant metastases is assessed clinically (including imaging) or pathologically at the time of diagnosis and before neoadjuvant therapy. Metastases are defined at diagnosis.

Further details are provided in Appendix.

2.3.2 Quality assurance of implementing Toronto staging

This research project will take a proactive stance towards standardisation on how different registries implement collection of stage according to the Toronto consensus guidelines.
We will:

- Maintain close liaison with ongoing international efforts to build an e-tool available to all PBCRs (this may occur as part of ENCR/JRC standard practice for the European Cancer Information System based at the European Commission's Joint Research Centre (JRC), Ispra https://ecis.jrc.ec.europa.eu/), as they are actively working to have the Toronto guidelines included in the electronic cancer staging tool for PBCRs personnel training.
- Create an anonymized set of real or fictional cases with source material and require all participating registries to stage these according to their processes.
- Hold on-line training workshops for all participating registry staff. Note that some have been held already in Nov 2020 as part of regular training for registries in childhood cancers by the European School of Oncology (ESO) and are available on-line.

- 1st event, 12 Nov 2020,
- https://www.e-eso.net/sessions/1727
- 2nd event, 19 Nov 2020,
- https://www.e-eso.net/sessions/1728

- Furthermore, encourage the use of a tool to facilitate the definition of stage by registrars for all cancer sites including the Toronto stage for paediatric cancers. This tool is available on-line at https://canstaging.org/tool?tnm_version=Toronto. The tool was developed by a collaboration between the Northern Ireland Cancer Registry (NICR), the International Agency for Research on Cancer (IARC), the Union for International Cancer Control (UICC), and Cancer Council Queensland (CCQ).

2.4 Structure of the case record to be submitted

For each tumour we will send a record template in Excel including the *compulsory* and the *optional* variables in one sheet and in a separate sheet the record template including the required and mandatory *additional indicators and information*. The PBCRs have to complete it according to the structure and the variables definitions indicated in Table 2 and described below.

2.4.1 Compulsory variables

Each record (case) includes demographic variables such as sex, year of birth, age at diagnosis in months, basis of diagnosis, plus information on examinations and the data sources used by the registrars for staging (see structure of the record, Table 2). If the tumour is a second or a third tumour, this fact should be reported. We ask to specify the International Classification of Childhood Cancers (ICCC-3) classification of previous tumours and the corresponding year of diagnosis. Tumour stage should be assigned by the PBCRs according to the Toronto consensus staging guidelines and associated implementation tools. PBCRs should use all available hospital data sources and procure input from relevant clinical staff when required to ensure consistent clinical interpretation of diagnostic investigations. Follow-up data (life status and time in days from diagnosis to death or last follow up) might be sent separately and at a later timepoint to ensure maximum completeness of follow up information.

2.4.2 Optional variables

In the JARC Pilot Study, the availability of information on **first line of treatment and recurrence or relapse** was already tested [7]**.** The JARC study showed that almost all participating PBCRs were able to collect this data item for both cancers. Furthermore, for treatment, if we exclude two countries that were not able to provide this information, 95% of Neuroblastoma and 84% of Wilms' cancer patients would have complete information. For those patients that had chemotherapy or radiotherapy, radiotherapy field and drug names were frequently reported for neuroblastoma. For Wilms tumour, these percentages were similar for the drug names but lower for the radiotherapy field (74%).

This project will therefore test how much information registries currently hold on these two important factors across all six tumour types (see Table 2). The rationale for collection of these additional variables is a feasibility assessment of how complete and with how much effort these additional factors can be provided by PBCRs. We will use this information for descriptive analysis of data availability, quality and completeness across the participating regions. The PBCRs are requested to report only the treatments included in the patient's planned

first line therapy. If a registry is not able to identify what is first line therapy, we recommend including all treatments given in the first 12 months following the date of diagnosis.
Knowledge of relapse/recurrence or progression of the disease is important for understanding the success of first line therapy. The latter is decided according to initial tumour stage and presence of other non-stage prognostic factors and requires data on relapse/recurrence or progression. We therefore ask PBCRs able to collect data on relapse/recurrence/progression to do so in order to understand the feasibility of this data item collection. It should be collected for all cases within the 3 years of follow-up.

Some **non-stage prognosticators** (NSP) for medulloblastoma, rhabdomyosarcoma, neuroblastoma and Wilms tumour are also requested if available [9]. No NSPs are currently recommended for collection for osteosarcoma and Ewing sarcoma. According to the JARC pilot study, for most registries the major source available for stage reconstruction was the clinical record of major hospital admissions, indicating NSP should be available for retrieval.
Even if they are not the major objective of the study, NSPs are important to better understand survival differences, as they characterize the behaviour of the tumour and are crucial for clinical risk stratification for treatment. Registries are asked whether it is possible for them to collect these items. Furthermore, **cause of death,** categorised as due to tumour, or toxicity, or comorbidity or other cause, is another optional variable. This categorization requires a clinical review of the information reported to the PBCR on causes of death, which may be multiple. This collection is also important to understand the feasibility of future specific studies that would test the hypothesis that there may be differences between countries in proportion of deaths ascribed to toxicity of treatment.

2.4.3 Additional indicators and information

2.4.3.1 Time taken to assign Toronto stage

We ask all PBCRs to send us an estimate of the additional effort (in approximate average minutes/case) currently required by the registry to obtain the Toronto stage for each specific tumour type.

2.4.3.2 Quality indicators

All PBCRs are required to submit in a default excel file the:

- % DCO (death certificate only) cases in the PBCR in the study period (calculated as: the number of children diagnosed by DCO, or autopsy/ number of children diagnosed with cancer)
- % NOS (not otherwise specified) in brain for children in the selected period: Number of morphology NOS in the brain (ICCC 3rd ed. III f) / number of cases in brain (ICCC 3rd ed. III)
- % NOS in kidney for children in the selected period: Number of morphology not otherwise specified in the kidney (ICCC 3rd ed. VI c) / number of cases in kidney (ICCC 3rd ed. VI)
- % NOS in soft tissue sarcomas (STS) for children in the selected period: Number of morphology NOS in the STS (ICCC 3rd ed. IX e) / number of cases in STS (ICCC 3rd ed. IX).
- %NOS in Bone Tumours for children in the selected period: Number of Unspecified malignant bone tumours (ICCC 3rd ed. VIII e) / number of cases with bones tumours (ICCC 3rd ed. VIII)
- % of neuroblastoma of the unknown primary sites: Number of neuroblastoma (ICD-O M-9500/3) and ganglioneuroblastoma (ICD-O M-9490/3) in C80.9 (unknown primary sites)/ ICCC 3rd ed IV a.

2.5 Identification of registries

All the European population-based registries have been invited to participate in the study. In addition, other non-European registries including Australia, Canada (Ontario), Brazil, Japan and Boston (USA) were invited as they are known to have the capability to reconstruct the requested Toronto stage and other prognostic variables. The 15 European countries who contributed data to the JARC pilot study [7], those who attended the JARC pilot study workshop held in Brussels - March 2018, have assured their participation. Both at the Brussels meeting and through the JARC study, registries stated that they could apply the Toronto consensus guidelines for tumour staging to their existing data, using their online and usual sources of data such as the pathological file and the hospital discharge administrative files. For a variable number of cases, the clinical hospital record is available as well. Also, all registries included in the EUROCARE-6 study (30 countries) have been invited to contribute.

Participating cancer registries will be population-based, either paediatric or general. Almost all the registries participating have already been checked by different stakeholders (organisation or specific project such as: IARC (https://iicc.iarc.fr/), ENCR, EUROCARE (http://www.eurocare.it/), ACCIS (https://accis.iarc.fr/) for quality indicators and this assures the expected completeness and quality of the information they collect for incidence and survival. There are a few exceptions among the PBCRs (Finland, Japan and Poland) and new checks will be carried out to ensure the coverage of these specific registries.

2.6 Data collection timelines

After the approval of the protocol from the participating registries and the expert partners involved in the study, we expect to collect the information within approximately 10 months, commencing from 1st July 2021. Due to the length of time to finalise the Data Transfer Agreement (DTA) with the large number of participating PBCRs, the timeline has been extended.

A centralised desk for information will be available at the INT Milan (tel. no. +39 02 23903518-3567) or Gemma Gatta and Laura Botta e-mail.

The final deadline for transmitting data, including final follow up data, to the INT is November 2022.

2.7 Quality checks

Data files will be checked with ad hoc developed procedures in regular use at the INT. For each tumour record, the validity of each variable, and of combinations of different variables (such as dates sequence, or ICD-O morphology and topography codes combinations, etc), will be checked to detect wrong/unlikely values.
The already existing JARC pilot study quality checks procedures will be updated to incorporate the newly included cancers.

The records flagged by the data checking process will be sent back to the registries for their revision/correction/confirmation. The INT portal will be used for these transmissions to and from the registries. This data quality checking process is the reason for retaining a pseudonymised link for each record, that can only be decoded by the cancer registry that submitted the record.

Cases ascertained only by the death certificates (DCO), number of cases diagnosed by cytology or histology (MV) and those with unspecified morphology codes (NOS) will be considered as data quality indicators for the diagnosis. The number of cases lost to follow-up and the number of those censored before the date of end of follow-up will be calculated and considered for the definition of quality of follow-up.

2.8 Statistical considerations

The main endpoints for the statistical analyses, by tumour type, are:

1. Differences in stage distribution between countries/regional groupings.

2. Survival differences between countries/regional groupings, and how much of any difference is explained by variations in stage distribution and/or survival by stage.

The formal statistical power to detect differences in stage distribution and survival rates between countries is necessarily limited by incident numbers of each of the six tumour types per country over the recent time period for which PBCRs are able to provide tumour stage. Therefore, analyses of stage distribution and survival rates for each tumour type per country will be descriptive, with 95% confidence intervals reported.

Approximately 8,000 cases will be included (table 2). As the study is population-based, these are the largest numbers available and are not biased in the ways that might affect institutional or clinical trial series.

Endpoint 1: To formally assess if differences in tumour stage at diagnosis are significant, we will group European countries according to the regional geographies used in EUROCARE 5 to achieve the group sizes necessary. Non-European jurisdictions will be considered individually. For expected case numbers by registry (table 2), we have approximately 60% power to detect a 10% difference in lower stages (localised, loco-regional) versus more advanced stage (metastatic) between two countries or regional groupings where there are 250 cases of each tumour type in each group (medulloblastoma, Wilms tumour). For group sizes with 300 cases (neuroblastoma), the power would be 70%. We will combine the sarcomas, who collectively comprise 29% of the cohort, for assessment of differences in stage distribution at diagnosis, according to the same country groupings.

Endpoint 2: Overall survival for each tumour type will be analysed for all patients and broken down by appropriate tumour stage, using standard Kaplan-Meier methods reported with 95% CIs. Survival differences between countries/regional groupings and how much is explained by variations in stage distribution will be studied by multivariable Cox regression including stage and other relevant prognostic variables (age at diagnosis, sex and/or primary site for at least some diagnostic groups), and confounders including stage migration.

3. Oversight and funding of the project

Day to day management of the project will be performed jointly by Gemma Gatta (assisted by Laura Botta) – Head of the Evaluative Epidemiology Unit, INT, Milan, and Prof Kathy Pritchard-Jones – Paediatric oncologist, University College London, UK. The more detailed project management plan is described in section 6.
Colleagues who led the development of the Toronto consensus staging guidelines have already developed an operational manual for their application that they have agreed to share with us and welcome our input into their further iteration as they are applied more widely. The manual has been translated from English to French, Italian, Portuguese and Spanish language and will be available to the registrars.

Webinars will be organized to disseminate and discuss the protocol. The European School of Oncology has already led two events and the recorded seminars are available on the web (see above). Further courses will be organized during 2021. An Italian initiative involving the Italian registries was held in February 2020 in Palermo and further national initiatives will be encouraged. Registries from the European regions speaking Latin languages (GRELL collaborative initiative, 2019-2020) will organise seminars/courses/workshop in their spoken languages.

The main funding for the project is provided by a peer-reviewed competitively awarded project grant from Children with Cancer UK (https://www.childrenwithcancer.org.uk/childhood-cancer-info/we-fund-research/projects-we-fund/understanding-why-childhood-cancer-survival-varies-between-countries/. This award includes a modest sum (estimated about £11 per case) for reimbursement to participating cancer registries for their efforts in sourcing and providing the Toronto staging data for the project. Prof Pritchard-Jones is the Principal Investigator, Dr Gemma Gatta is a named Co-Investigator. Prof Pritchard-Jones is responsible for reporting to the funder. Dr Gatta has obtained additional funds to support participation of the Italian cancer registries.

4. Ethical approval, research governance and GDPR compliance (confidentiality and data processing)

Ethical approval for the project has been given by the Research Ethics Committee of University College London on 22nd April 2021 and is valid until 30th June 2024. Also, the Ethical Committee of the Fondazione IRCCS "Istituto Nazionale dei Tumori" approved the project during the e-session on 25th May 2021.
A copy of the UCL REC approval letter is included in the appendix.

Additional approvals that may be required at the national or regional level by the other participating PBCRs will be requested from their applicable competent ethical or regulatory authorities, according to national regulations. If a PBCR needs a Data Transfer Agreement – a formal contract that clearly documents what data are being transferred and how the data can be used – it will be stipulated, agreed and signed directly between the parties (INT and each CR). Please write a formal request by email to benchista@istitutotumori.mi.it, describing the requirements of your cancer registry and the name of the legal /administrative contact in your institution. This process will facilitate the contact with the legal entity of the Fondazione IRCCS "Istituto Nazionale dei Tumori" of Milano who will provide a template for the agreement.

Participating PBCRs will be responsible for ensuring these approvals are in place and for their collection and sharing of detailed pseudonymized clinical data according to the rules that ensure patient confidentiality, and which are GDPR-compliant. This includes having the responsibility of Data Controller for the data they submit to the project.

The BENCHISTA Project Working Group includes representation from all PBCRs contributing data to the project, as well as tumour-specific clinical leads from the relevant European clinical trials groups, parent and patient representation and the principal investigators at UCL and INT, Milan. The format of the data items to be collected has been agreed with the PBCRs to be in the maximally de-identified format that minimises any risks to data privacy, in compliance with GDPR. UCL and INT will act as joint Data Controllers for the project, with responsibilities as defined by article 26, GDPR and with the legal basis for data processing under article 6, GDPR 2018 being "Public interest" (clause (e)) and article 9 par.2 clause (j) and (i)"pub; art. 12 of DIRECTIVE 2011/24/EU;article 168, p.2, of Treaty on the Functioning of the European Union. Only INT has access to pseudo anonymised personal data and UCL does not.

The INT rules for the management of the project data base will be used for the analyses:

1- INT will receive pseudo-anonymised records from registries in xlsx format (; as delimiter).
2- Data will be transferred to INT using the secure platform *Microsoft SharePoint* or any other secure platform required by the PBCRs to comply with their data protection laws.
3- The database will be part of the INT computer system, and its storage and access will follow the rules already adopted by INT (see appendix for Data safety details).
4- Only personnel authorized and involved in the project will access the database based in Milan.
5- Database will be managed in Excel and then Stata used for the analyses.
6- The analyses will cover the objectives of the project and possible related issues.
7- The analyses may last at least 5 years if further follow up information is available and/or to address any queries from referees during submission of project manuscripts for peer reviewed publication.

8- After 10 years from project initiation (i.e., January 2031), the database will be deleted unless further requests for data analysis have been requested and the necessary approval obtained from the data providers and the project governance approvers of UCL and INT.

The BENCHISTA data remain the property of the contributing registries, whose consent is required before they can be used for purposes other than those originally envisaged in the BENCHISTA protocols. All members of the Working Group that provide data must be informed of any analysis being carried out.
PBCRs will send the dataset to the analytical team at the epidemiology research group in the National Tumour Institute, Milan, Italy, who will check the quality data, calculate and compare stage at diagnosis and survival rates between countries. The association between variation in tumour stage and survival differences will be tested. Further variables such as NSP and recurrences will be evaluated and may be used in analyses according to their completeness.

This document (BENCHISTA Final Protocol, version 4.4) should be used as the final protocol describing the work to be undertaken to assess the feasibility of applying the Toronto staging guidelines on population-based cancer registry data and organising the collection of tumour stage by European cancer registries in a routine way.

The list of the procedures for security measures (both technical and organizational) implemented at the INT are summarized in the appendix.

5. Outcome and Publication Policy

The main output from this project will be the publication of stage distribution and survival by stage for childhood cancer patients. Geographical differences will be presented by (large) country or, depending on sample size, by geographical region. This will maximise statistical robustness and will minimise the risks to data privacy. Analyses according to other major variables such as recurrence, treatment and NSP will be considered according to the completeness of these variables.

6. Project Management

One participant for each contributing registry will be member of the overall Project Working Group (PWG). PBCRs contributing more than 50 cases will identify two persons to be included in the PWG. It is the population-based cancer registry directors' responsibility to define the PWG member for each PBCR and to inform the project leaders regarding the correct email contact for their participants. In addition, a lead oncologist for each tumour type will be nominated from the relevant tumour-specific European clinical trial groups.

This PWG will finalise the detailed data collection and analysis protocol, obtain ethical approval in each country and support each registry in accessing the necessary data linkage from clinical registries and routine hospital information systems. PWG members will receive regular updates on the project's progress and will always be included as a named working group in each publication regarding the project This group will convene quarterly online. All PWG members will be able to make the most of the capabilities of this database; if a member of the working group has a new paper proposal that could use the project database, it will be circulated with the PWG. If no negative feedback comes back from the Project Management Team (PMT) within one month, this will be taken as a positive reply from all the registries.
The PMT comprises the research leaders in the UK and Italy with a smaller number of nominated representatives from the PWG. This will convene bi-monthly throughout the project (Table 1 and Figure 1).

Table 1. Project Management Team

PMT members	Country	Affiliations
Kathy Pritchard-Jones	UK	UCL Great Ormond Street Institute of Child Health, University College London, UK
Gemma Gatta	Italy	Research Department, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy
Laura Botta	Italy	Research Department, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy
Fabio Didonè	Italy	Research Department, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy
Angela Lopez	UK	UCL Great Ormond Street Institute of Child Health, University College London, UK
Charles Stiller	UK	National Cancer Registration and Analysis Service, Public Health England, London, United Kingdom
Bernward Zeller	Norway	Division of Pediatric and Adolescent Medicine, Oslo University Hospital, Oslo, Norway
Zsuzsanna Jakab	Hungary	Department of Pediatrics, Semmelweis University, Budapest, Hungary
Adela Cañete	Spain	Paediatric Oncology and Hematology Unit, Hospital U I P La Fe, Valencia, Spain
Lisa Lyngsie Hjalgrim	Denmark	Department of Pediatrics and Adolescent Medicine, University of Copenhagen, Rigshospitalet, Copenhagen, Denmark

We have established an Independent Advisory Board (IAB) that includes a cancer registry director not directly involved in the day-to-day project, parent and survivor representatives, clinical executive level members of a national paediatric oncology society, a clinical trial study group and a medical director-level clinician involved in organisation of childhood cancer services.

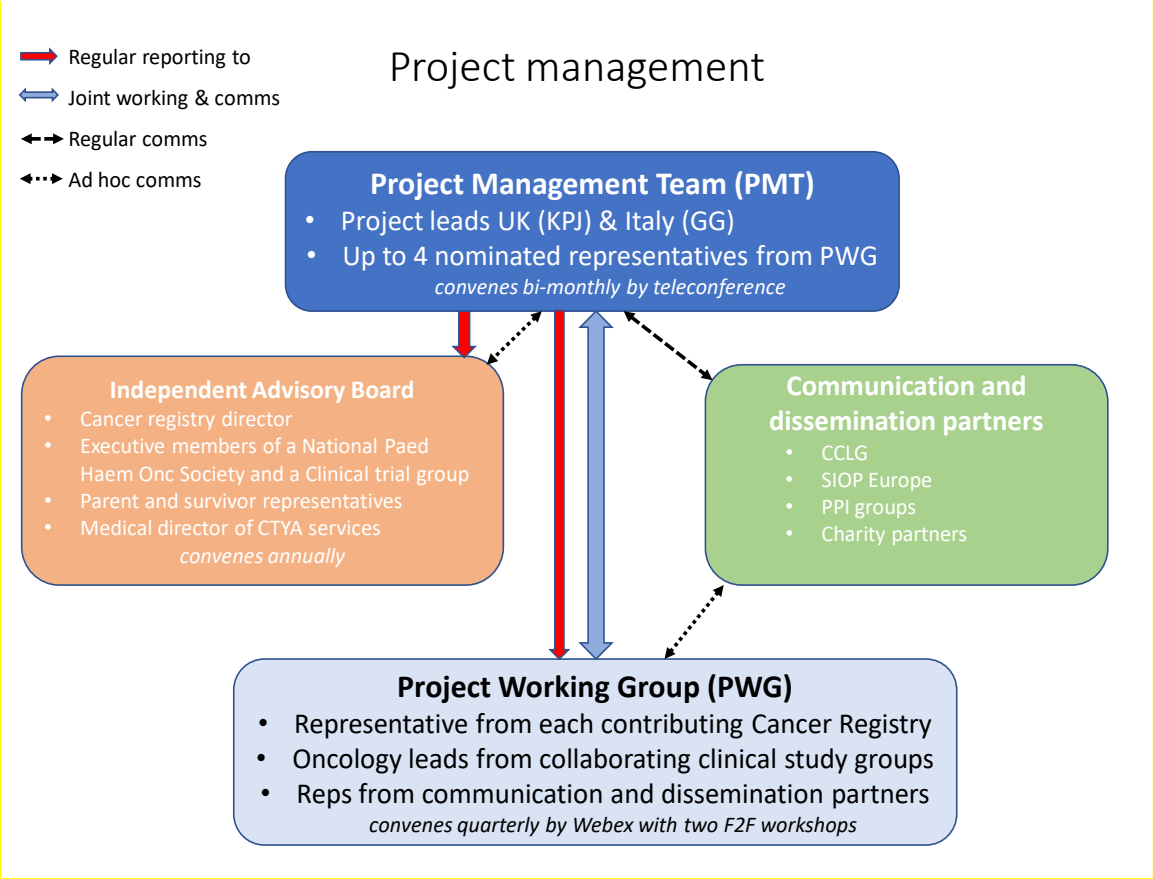
Prof Joanne Aitken – Head of Research and Director, Cancer Registries, Cancer Council Queensland, who leads the Australian children's cancer registry, and who has already tested TG implementation in Australia, is co-chair of this Independent Advisory Board; together with Prof Anna Gavin – Queen's University Belfast, Director of the Northern Ireland cancer registry and member of the ENCR steering committee.
The full membership of the advisory board is mentioned below:

Table 2. Independent Advisory Board

Independent Advisory Board members	Country	Affiliation
Joanne Aitken (co-chair)	Australia	Cancer Council Queensland, Queensland, Brisbane, Australia
Anna Gavin (co-chair)	UK	Northern Ireland Cancer Registry School of Medicine, Centre for Public Health, Queen's University Belfast, Belfast, United Kingdom
Francois Doz	France	SIREDO Center (pediatric, adolescent and young adults oncology), Institut Curie, University of Paris, Paris, France
Riccardo Haupt	Italy	Epidemiology and Biostatistics Unit and DOPO Clinic, IRCCS Istituto Giannina Gaslini, Genova, Italy
Wendy Tarplee-Morris	UK	The Little Princess Trust Hereford, England, United Kingdom
Christian Müller	Germany	Gert und Susanna Mayer Stiftung, Wuppertal, Nordrhein-Westfalen, Germany
Martin McCabe	UK	Division of Cancer Sciences, University of Manchester, Manchester, United Kingdom
Piotr Czauderna	Poland	Department of Surgery and Pediatric Urology, Medical University of Gdansk
Carmen Martos	Italy	European Commission, Joint Research Centre, Ispra, Varese, Italy

The relation and the composition of each group involved in the project are shown in the following figure.

Figure 1. Project Groups and workflow



6.1 Communication and dissemination

We will work closely with SIOP Europe (https://siope.eu/), the Children's Cancer and Leukaemia Group (CCLG, https://www.cclg.org.uk/) in the UK and equivalent national professional societies to announce the project and keep relevant communities updated on progress and results through their websites, newsletters and social media (see letters of support). This will include working with tumour-specific parent-patient involvement in research (PPIE) groups such as the Wilms Tumour Link Group. Preliminary results will be submitted as conference abstracts in 2022 and final results will be presented at an impactful global cancer conference in 2022 or 2023 and submitted for publication.

7.Participating registries

Austrian Cancer Registry
Belgian Cancer Registry
Bulgarian Cancer Registry
Croatian Cancer Registry
Czech National Cancer Registry
Danish Childhood Cancer Registry and Department of Pediatric Oncology
Estonian Cancer Registry
National Registry of Childhood Solid Tumours, France
NARECHEM-ST, Greece
German Childhood Cancer Registry (Mainz)
Hungarian Child Cancer Registry
National Cancer Registry Ireland
Italian registries
- Liguria CR, Ospedale Policlinico San Martino IRCCS, Italy
- Piemonte Childhood Cancer Registry, Italy
- Varese and Como Cancer Registry, ATS Insubria, Italy
- Bergamo Cancer Registry, Italy
- Monza and Brianza Cancer Registry, Italy
- ATS Metropolitan city of Milan Cancer Registry, Italy
- Cremona and Mantova Cancer Registry, ATS Valpadana, Italy
- Alto Adige Cancer Registry, Italy
- Trento Cancer Registry, Italy
- Friuli Venezia Giulia Cancer Registry, Italy
- Veneto Cancer Registry, Italy
- Emilia-Romagna Cancer Registry, section of Modena, Italy
- Emilia-Romagna Cancer Registry, section of Parma, Italy
- Emilia-Romagna Cancer Registry, section of Reggio Emilia, Italy
- Emilia-Romagna Cancer Registry, section of Romagna, Italy
- Emilia-Romagna Cancer Registry, section of Piacenza, Italy
- Emilia-Romagna Cancer Registry, section of Ferrara, Italy
- Toscana Cancer Registry, Italy
- Marche Childhood Cancer Registry, Italy
- Umbria Cancer Registry, Italy
- Latina Cancer Registry, Italy
- Molise Cancer Registry, Italy
- Campania Childhood Cancer Registry, Italy
- Cancer registry of Puglia, Section of Childhood and Adolescence cancer, Italy
- Basilicata Cancer Registry, Italy
- Reggio Calabria, Catanzaro, Cosenza and Crotone Cancer Registries, Italy
- Palermo Cancer Registry, Italy
- Ragusa and Caltanissetta Cancer Registry, Italy
- CT-ME-EN Integrated Cancer Registry, Italy
- Siracusa Cancer registry, Italy
- Sassari Cancer Registry, Italy
- Nuoro Cancer Registry, Italy
- Cagliari Cancer Registry, Italy

Lithuanian Cancer Registry
Malta National Cancer Registry, Health Information and Research
Norwegian Cancer Registry
Swedish Childhood Cancer Registry
National Poland Registry
Portuguese Cancer Registry
The Oncology Institute "I. Chiricuta", Romanian Cancer Registry
Slovakian National Cancer Registry
Cancer Registry of Republic of Slovenia
Spanish registries
    Basque Country, Euskadi-CIBERESP Cancer registry, Spain
    Childhood and Adolescents Cancer Registry - CISCV, Spain
    Girona CR, CIBERESP, ICO, IDIBGI, Spain
    Registro de Cáncer de Granada , EASP, CIBERESP, ibs.GRANADA, UGR, Spain
    Murcia Cancer registry, CIBERESP, IMIB-Arrixaca, Spain
    Registro de Cáncer de Navarra-CIBERESP, Spain
    Spanish Registry of Childhood Tumours (RETI-SEHOP), Spain
    Tarragona Cancer registry, Spain
Childhood Switzerland Cancer Registry
The Netherlands Cancer Registry
UK registries
    Public Health England National Cancer Registration & Analysis Service PHE/NCRAS). National Disease Registration Service transferred from PHE to NHS Digital on 1 October 2021.
    Northern Ireland Cancer Registry
    Public Health Scotland, Scotland Cancer Registry
    Welsh Cancer Intelligence and Surveillance Unit, Welsh Cancer Registry
Center for Cancer Registries, National Cancer Center, Japan
Osaka International Cancer Institute, Japan
Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital, Japan
Brazilian population-based Cancer registry, Brasil
POGO Pediatric Oncology Group of Ontario, Canada
Australian Childhood Cancer Registry
Boston Children's Hospital/Dana-Farber Cancer Institute, USA

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Table 3. Estimated number of cases for 3 years for the 6 cancers included in the project by PBCR

Country	CRs	III(c) Intracranial and intraspinal embryonal tumors (0-14 years)	IV(a) Neuroblastoma and ganglioneuroblastoma (0-14 years)	VI(a) Nephroblastoma and other nonepithelial renal tumors (0-14 years)	VIII(a) Osteosarcomas (0-19 years)	VIII(c) Ewing tumor and related sarcomas of bone (0-19 years)	IX(a) Rhabdomyosarcomas (0-19 years)
Austria	AT_Austria National	29	42	28	28	20	25
Belgium	BE_Belgium National	41	65	45	42	32	33
Bulgaria	BG_Bulgaria National	20	24	19	17	18	17
Croatia	CR_Croatia National	17	24	18	15	13	14
Cyprus	CY_Cyprus National	2	2	1	3	2	3
Czech Republic	CZ_Czech Rep.National	21	35	19	20	22	18
Denmark	DK_Denmark National	21	25	17	15	16	15
Estonia	EE_Estonia National	5	5	4	4	3	3
Finland	FI_Finland National	20	26	22	12	5	15
France	FR_France National, Childhood	249	425	288	117	113	180
Germany	GE_Germany National, Childhood	224	336	292	175**	157**	179**
Greece	GR_Greece National, Childhood	15	64	37	18	20	22
Hungary	HU_Hungarian National, Childhood	43	70	37	16	17	15
Iceland	IC_Iceland National	1	1	1	2	0	1
Ireland	IR_Ireland National	20	30	23	14	11	18
Italy	IT_Alto Adige/Sud Tirolo	2	2	1	2	1	1
	IT_ Puglia	9	20	14	9	12	9

IT_Basilicata	2	1	1	1	1	0
IT_Bergamo	3	8	2	3	3	4
IT_Biella	1	0	0	1	0	0
IT_Brescia	3	6	4	3	2	2
IT_Catania-Messina-Siracusa-Enna	5	10	5	5	3	6
IT_Catanzaro	2	1	1	0	1	0
IT_Insubria Varese Como	2	3	2	1	2	2
IT_Cremona	1	2	2	0	2	1
IT_Ferrara	1	1	1	0	1	1
IT_Firenze-Prato	5	6	3	3	2	2
IT_Friuli Venezia Giulia	1	6	4	2	2	2
IT_Genova	2	5	2	3	1	1
IT_Latina	3	3	2	1	2	2
IT_Lodi	0	3	2	2	2	3
IT_Mantova	1	2	2	1	1	1
IT_Milano	-	-	-	-	-	-
IT_Modena	2	6	1	1	2	3
IT_Monza e Brianza	2	3	3	2	4	3
IT_Napoli	4	7	3	3	3	2
IT_Nuoro	0	1	0	1	0	0
IT_Palermo and Province CR (PPCR)	2	8	4	2	3	2
IT_Parma	2	3	2	1	1	1
IT_Piacenza	0	1	0	1	0	0
IT_Piemonte, Childhood	14	28	13	13	8	10
IT_Ragusa	7	1	2	0	0	0
IT_Reggio Emilia	2	3	2	2	2	0

	IT_Romagna	3	6	5	3	3	3
	IT_Salerno	2	3	3	4	4	3
	IT_Sassari	1	1	1	1	0	1
	IT_Siracusa	0	1	2	1	1	1
	IT_Sondrio	0	0	0	1	0	0
	IT_Trapani	2	1	1	0	1	1
	IT_Trento	1	2	1	1	0	1
	IT_Umbria	3	5	3	3	2	2
	IT_Veneto	7	13	4	4	6	5
	IT_Viterbo	1	2	1	1	0	1
Latvia	LV_Latvia National	4	7	6	7	2	5
Lithuania	LT_Lithuania National	7	13	12	9	8	9
Malta	ML_Malta National	2	2	3	1	1	2
Norway	NO_Norway National	24	22	20	17	10	13
Poland	PL_Poland National	117	136	119	86	68	86
	PT_Central Portugal	9	8	6	4	3	5
Portugal	PT_North Portugal	10	23	13	9	10	11
	PT_South Portugal	17	25	18	13	8	15
Slovakia	SK_Slovakia National	20	28	23	22	16	15
Slovenia	SL_Slovenia National	7	5	7	6	4	6
	SP_Balearic Islands	2	4	5	3	3	2
	SP_Basque Country	7	13	6	5	5	5
	SP_Canarie	3	8	5	4	3	6
	SP_Castellon (general)	3	2	1	2	3	3
Spain	SP_Com_Valenciana, Childhood	17	28	13	11	12	13
	SP_Girona	2	4	2	3	2	2
	SP_Granada	3	5	4	3	3	3
	SP_Murcia	6	8	5	5	5	4
	SP_Navarra	3	4	3	2	2	2

	SP_RETI-SEHOP (Ba_Ma), Childhood	34	63	36	15	26	22
	SP_Tarragona	3	6	3	2	3	2
Switzerland	SW_Switzerland National, Childhood	27	34	27	14	13	22
The Netherlands	NL_The Netherlands National	66	74	74	61	44	52
England	UK_England National	157	226	213	156	100	156
Northern Ireland	UK_Northern Ireland National	8	8	7	5	6	8
Scotland	UK_Scotland National	19	23	16	15	17	19
Wales	UK_Wales National	11	13	11	10	6	9
Italy	Campania*	21	37	22	11	11	13
Italy	Pavia*	2	3	2	1	1	1
Canada	Canada*	-	-	-	-	-	-
Romania	Romania*	84	129	66	31	27	25
Australia	Australia*	99	135	105	42	45	69
Japan	Japan*	53	96	33	13	11	37

*Not in EUROCARE 6
**0-17 years old
'-' Number of cases not known

Table 4. Structure of the record

Variable	No. of characters	Notes and encoding
Basic variables		
Registry	10	alphabetic
Registry Patient Identification code	10	assigned by the registry, it is a project-specific pseudonymised code
Year of birth	4	yyyy
Age at diagnosis	3	Numeric (in months)
Year of diagnosis	4	yyyy
Sex	1	boy/girl/unknown 1/2/9
Base of diagnosis (as coded in the ENCR protocol)	1	DCO/Clinical/Clinical investigation/Specific tumour markers /Cytology/Histology of a metastasis/Histology of a primary tumour /Unknown 0/1/2/4/5/6/7/9
ICDO-3-Topography	3	Only the numeric part of the ICD-O-3 topography code will be reported (the "C" and "." will not be included)
ICDO-3-Morphology	4	Malignant, only, behaviour=3
First previous cancer	1	Y/N/unknown 1/0/9
First previous cancer definition		International Classification of Childhood Cancers (ICCC) 3rd edition
Year of diagnosis of the first previous cancer	4	yyyy / 9
Second previous cancer	1	Y/N/unknown 1/0/9
Second previous cancer definition		International Classification of Childhood Cancers (ICCC) 3rd edition
Year of diagnosis of the second previous cancer	4	yyyy / 9
Imaging/examination used for staging before any treatment		
CT/ MRI primary site	1	Y/N/unknown 1/0/9
MRI whole neuraxis	1	Y/N/unknown 1/0/9
MRI whole neuraxis outcome		Negative/Positive/Suspicious/Unknown 0/1/2/9
CT thorax	1	Y/N/unknown 1/0/9
CT thorax outcome		Negative/Positive/Suspicious/Unknown 0/1/2/9
Imaging of regional lymph nodes	1	Y/N/unknown 1/0/9
Imaging of regional lymph nodes outcome		Negative/Positive/Suspicious/Unknown 0/1/2/9
CSF	1	Y/N/unknown 1/0/9
CSF outcome		Negative/Positive/Suspicious/Unknown 0/1/2/9
MIBG scan	1	Y/N/unknown 1/0/9
MIBG scan outcome		Negative/Positive/Suspicious/Unknown 0/1/2/9
Abdominal ultrasound	1	Y/N/unknown 1/0/9
Abdominal ultrasound outcome		Negative/Positive/Suspicious/Unknown 0/1/2/9
Bone scan	1	Y/N/unknown 1/0/9
Bone scan outcome		Negative/Positive/Suspicious/Unknown 0/1/2/9
Bone marrow aspirate or biopsy	1	Y/N/unknown 1/0/9

Bone marrow aspirate or biopsy outcome		Negative/Positive/Suspicious/Unknown 0/1/2/9
x-ray thorax	1	Y/N/unknown 1/0/9
x-ray thorax outcome		Negative/Positive/Suspicious/Unknown 0/1/2/9
PET	1	Y/N/unknown 1/0/9
PET outcome		Negative/Positive/Suspicious/Unknown 0/1/2/9
Tissue biopsy	1	Y/N/unknown 1/0/9
Tissue biopsy outcome		Negative/Positive/Suspicious/Unknown 0/1/2/9
Source used for staging		
Clinical report (hospital clinical records)	1	Y/N/unknown 1/0/9
Pathological report	1	Y/N/unknown 1/0/9
Administrative files (hospital discharge, etc.)	1	Y/N/unknown 1/0/9
Clinical study group	1	Y/N/unknown 1/0/9
Others (string)	10	alphabetic
Toronto staging, Neuroblastoma		
Stage Tier 1	2	L/LR/M/MS/X 1/2/3/4/9
Stage Tier 2	2	L1/L2/M/MS/X 1/2/3/4/9
Laterality	1	Not applicable/Right/Left/Unilateral NOS/Bilateral//unknown 0/1/2/3/4/9
* NSP: N-Myc	1	Amplified Y/N (exact definitions to be discussed)
Toronto staging, Wilms tumour		
Stage Tier 1 after pre-surgery chemotherapy	1	L/M/X 1/2/9
Stage Tier 2 after pre-surgery chemotherapy	1	y-I/y-II/y-III/IV/9 1/2/3/4/9
Stage Tier 1 after immediate surgery (i.e., surgery first)	1	L/M/X 1/2/9
Stage Tier 2 after immediate surgery	1	I/II/III/IV/X 1/2/3/4/9
Laterality	1	R/L/B 1/2/3
O_NSP: Wilms Presence of anaplasia	1	No/Yes, but unknown if focal or diffuse/Yes, focal/Yes, diffuse/ Anaplasia unknown 0/1/2/3/9
Toronto staging, Medulloblastoma		
Stage Tier 1	1	L/M/X 1/2/9
Stage Tier 2	2	M0/M1/M2/M3/M4/X 0/1/2/3/4/9
* Evaluation of postoperative residual disease		R0/R1/R2/R+/unknown 0/1/2/3/9
*_NSP: Wingless (WNT) medulloblastoma	1	Y/N/unknown 1/0/9
*_NSP: Sonic Hedgehog (SHH) medulloblastoma	1	Y/N/unknown 1/0/9
Toronto staging, Osteosarcoma, Ewing sarcoma		
Stage Tier 1	1	L/M/X 1/2/9
Stage Tier 2	1	L/M/X 1/2/9
Toronto staging, Rhabdomyosarcoma		
Stage Tier 1	1	L/M/X 1/2/9
Stage Tier 2	1	I/II/III/IV/X 1/2/3/4/9
*_NSP: FKR-PAX3 rhabdomyosarcoma	1	Y/N/unknown 1/0/9
*_NSP:FKR-PAX7 rhabdomyosarcoma	1	Y/N/unknown 1/0/9

Primary Treatment defined as given within 1 year from diagnosis		
*_Surgery	1	Y/N/unknown 1/0/9
*_Chemotherapy	1	Y/N/unknown 1/0/9
*_Chemotherapy type	1	Preoperative chemo/Postoperative chemo/Both, preoperative and postoperative chemo/Chemotherapy only/ Unknown 1/2/3/4/9
*_Radiotherapy	1	Y/N/unknown 1/0/9
*_Relapse/recurrence/progression		
*_Relapse/ recurrence/ progression	1	Y/N/unknown 1/0/9
*_Time in days from diagnosis to relapse/recurrence/progression		numeric
Follow-up		
Status of life alive/dead	1	alive/dead/unknown 1/2/9
*_Causes of death (CoD)	1	Toxicity of treatment, Tumour, Comorbidity previously present in the child, Others, unknown 1/2/3/4/9
Time in days from diagnosis to death or last follow up		numeric

* Are optional variables

Separate sheet of the excel file including:

- Estimate of an average time (in minutes) to stage a patient with Medulloblastoma
- Estimate of an average time (in minutes) to stage a patient with Osteosarcoma
- Estimate of an average time (in minutes) to stage a patient with Rhabdomyosarcoma
- Estimate of an average time (in minutes) to stage a patient with Ewing sarcoma
- Estimate of an average time (in minutes) to stage a patient with Neuroblastoma
- Estimate of an average time (in minutes) to stage a patient with Wilms tumour

QUALITY CHECKS, to be collected by the PBCRs

- %DCO cases in the PBCR in the study period (calculated as: the number of children diagnosed by DCO, or autopsy/ number of children diagnosed with cancer)
- % not otherwise specified (NOS) in brain for children in the selected period: Number of morphology NOS in the brain (ICCC 3rd ed. III f) / number of cases in brain (ICCC 3rd ed. III)
- %NOS in kidney for children in the selected period: Number of morphology not otherwise specified in the kidney (ICCC 3rd ed. VI c) / number of cases in kidney (ICCC 3rd ed. VI)
- %NOS in Soft Tissue Sarcomas (STS) for children in the selected period: Number of morphology NOS in the STS (ICCC 3rd ed. IX e) / number of cases in STS (ICCC 3rd ed. IX)
- %NOS in Bone Tumours for children in the selected period: Number of Unspecified malignant bone tumours (ICCC 3rd ed. VIII e) / number of cases in bones (ICCC 3rd ed. VIII)
- % of neuroblastoma of the unknown primary sites: Number of neuroblastoma (ICD-O M-9500/3) and ganglioneuroblastoma (ICD-O M-9490/3) in C80.9 (unknown primary sites)/ ICCC 3rd ed IV a