JARC WP4 and WP7: Evaluate how the "Toronto principle and guidelines "providing recommendations on which staging systems should be adopted by population-based cancer registries for major childhood malignancies".

Protocol of the Pilot Study (3nd version, Dec, 20, 2017)

Background and aim of the study

Within the WP 4 (Epidemiology), in collaboration with WP7 (task 2) of the European Joint Action on Rare Cancers (JARC)[1], a pilot study will test how the Toronto paediatric cancer staging recommendations [2] can be adopted by population-based cancer registries to undertake analysis on survival by tumour stage in one or more major childhood solid tumour types. Childhood cancers are all rare cancers. The more recent EUROCARE study showed large geographical disparities continue within Europe and that there is progress during the time period [3]. Both time and space outcome differences can be explained by changes in tumour stage at presentation. A standardised way to collect stage and a complete collection of this variable by cancer registries is crucial for comparison and interpretation of the outcome differences.

Recently the "Toronto consensus principles and guidelines" provided recommendations on which staging system should be adopted by population-based cancer registries for each of the major childhood malignancies [2].

Pilot investigations are needed to assess the feasibility of these recommendations thus a pilot study aimed at assessing the feasibility of using the Toronto guidelines in European cancer registries is the objective of this study.

Methodology

Selection of tumour types for the pilot study

Among the 18 childhood cancers included in the Toronto guidelines, we selected two important solid cancers: neuroblastoma and Wilms tumour. Table 1 provides the expected annual number of cases for the selected cancers, from the RARECAREnet search tool [4], diagnosed in European cancer registries/countries. The expected number was calculated as an average of the 2000-2007 diagnosed cases. We identify these tumours because: 1) of the good prognosis (Wilms tumour, neuroblastoma) and curability (access to cure), 2) of the important differences in cancers survival, 3) they represent two relatively common childhood cancers and 4) can be representative of the difficulties in the collection of information.

General rules of staging

Stage is defined as extent of disease at the time of diagnosis and is based on evidence acquired before treatment (with the exception of Wilms tumour, see table 3).

For all diagnostic groups including Wilms tumour, the presence of **distant metastases** is assessed clinically or pathologically at the time of diagnosis and before neoadjuvant therapy.

The presence of **bilateral disease** should also be noted at the time of diagnosis, in the general data field for this item, which is recorded separately from stage.

Table 1: number of expected annual cases by country (cases <15 years of age) for neuroblastoma and Wilms tumour

Country / Cancer entity	No. of expected new cases * **Neuroblastoma**	**Wilms tumour**
	annual number	
Austria National	14	9
Belgium Flanders	10	11
Bulgaria National	8	6
Croatia National	8	6
Denmark National	9	4
Estonia National	1	1
Finland National	9	7
France National, Childhood ST	136	92
Germany National, Childhood	134	100
Hungarian National, Childhood	22	11
Iceland National	1	<1
Ireland National	9	7
Italy, partial	42	22
Latvia National	2	1
Lithuania National	4	3
Malta National	1	1
Norway National	7	7
Poland, partial	5	5
Portugal, partial	9	4
Slovakia National	7	7
Slovenia National	2	3
Spain, partial	32	13
Sweden National	12	14
Switzerland, Childhood	14	9
The Netherlands National	24	29
England-Wales National, Childhood	70	69
Northern Ireland National	2	3
Scotland National	7	6
European pool	597	454

* This is a mean of the diagnosed cases 2000-2007 *Data from www.rarecarenet.eu*

Neuroblastoma.

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

The definition of stage has to be **at the time of diagnosis, prior to any surgical resection**.

Imaging necessary for the definition of stage are CT, MRI and scintigraphy, therefore information for staging are included in the report of imaging. They are crucial to assess the invasion of vital structures. The list of vital structures is in the appendix below. Bone marrow aspirates and biopsies have to be performed to evaluate whether a marrow infiltration is present in neuroblastoma. See Table 2 for the staging of neuroblastoma by the Toronto guidelines which follows those of the INRG group [5]. Four risk strata are recognised: loc 1, loc 2, M+ and MS. Briefly, loc 1 and loc 2 differ for the invasion of vital structures. Metastases are divided into two strata based on age and on involvement of specific organs (see appendix). Toronto guidelines suggest the use of two tiers for each cancer staging, tier 1 and 2, based on the appropriate data access and resources available to registry. The proposal is to permit all the registries to provide a comparable information on stage, according to the level of clinical date they can acquire.

Table 2: staging system for **neuroblastoma** (Toronto guidelines)

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 vital structures as defined by the list of IDRFs (i.e. there are no IDRFs.) 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 (ie, 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 (ie, 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 a 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 in patients ≤ 18 months (547 days) with metastases confined to skin, liver, and/or bone marrow. .	**Stage MS**	Metastatic disease in patients ≤ 18 months (547 days) with metastases confined to skin, liver, and/or bone marrow. MIBG scintigraphy must be negative in bone and bone marrow.

IRDF =Image-defined risk factors

Wilms tumour.

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

In Wilms tumour, where a case is treated with pre-operative chemotherapy, the overall tumour stage (metastatic or localised) should be documented at diagnosis, prior to any chemotherapy. The more detailed abdominal tumour stage in localised tumours should be documented following subsequent nephrectomy and the prefix 'y' used (see table 3). Bilateral cases (stage V) should have their bilaterality confirmed in the general data field for this item, which is recorded separately from stage. In cases of bilateral disease, the stage of the most advanced kidney should be recorded for tumour stage, or stage IV if there are metastases.

The major imaging modalities used to assess tumour stage are the abdominal ultrasound examination, cross-sectional computed tomography (CT) or magnetic resonance imaging (MRI) scans of the abdomen and CT scan thorax and/or chest radiograph. 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 3). 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 also 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.

There are two different approaches (SIOP and COG/NWTSG) [6] to staging systems that are based both on postoperative pathological features and findings for tumour extent (stages I to III) but which differ in how they apply histological features and molecular biomarkers into risk stratification. SIOP stage is based on the findings at surgery after the patient has received neo-adjuvant chemotherapy. For this malignancy, the use of the TNM y prefix should be

adopted for staging of the abdominal tumour. The y prefix denotes the fact that stage was identified after neoadjuvant chemotherapy was given: for example, a y-stage II would be equivalent to a SIOP stage II (Table 3). Both groups recognise the presence of metastatic (stage IV) disease at diagnosis, based on imaging findings. ONLY ONE TYPE OF STAGE HAVE TO BE FILLED IN (pre or post chemotherapy and on surgical specimen).
Efforts to encourage institutions and cooperative trial groups to collect data based on preoperative imaging irrespective of what staging system was used to identify treatment would be welcome.

Table 3: staging system for Wilms tumour (COG and SIOP protocol)

Staging system for Wilms tumour for patients who <u>have not</u> received chemotherapy prior to surgery (Children's Oncology Group (COG) protocol)	
TIER 1	**TIER 2**
Localized No distant metastatic disease	**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 penetrates 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 nonhaematogenous 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 fine-needle aspiration) prior to removal of kidney • Resection margins involved by tumour
Metastatic Distant metastatic disease	**Stage IV** Haematogenous metastases or spread beyond abdomen

<table>
<tr><th colspan="3">Staging system for Wilms tumour for patients who have received chemotherapy prior to surgery (International Society of Paediatric Oncology (SIOP) protocol)</th></tr>
<tr><th colspan="2">TIER 1</th><th>TIER 2</th></tr>
<tr><td>Localized</td><td>No distant metastatic disease</td><td>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</td></tr>
<tr><td></td><td></td><td>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</td></tr>
<tr><td></td><td></td><td>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)</td></tr>
<tr><td>Metastatic</td><td>Distant metastatic disease</td><td>Stage IV

Haematogenous metastases or spread beyond abdomen at diagnosis.</td></tr>
</table>

Identification of registries

First, we will invite registries from the MSs partners of the JARC. We already contacted registries from Belgium, France, Spain, the Netherlands, Italy, Slovenia and the UK. Other registries outside JARC will be invited as well. All these registries have already met, last year two meetings in Valencia (Spain) and Baveno (Italy) at the RARECAREnet project meeting and ENCR annual assembly, respectively. 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.

Table 1 provides the expected annual cases for the two cancers by registry/country, they are calculated from incidence 2000-2007, from EUROCARE/RARECAREnet projects.

Eligible cases, time period and numbers to be staged

On the basis of the expected annual number of cases according to registry/country size (Table 1), we propose that **smaller registries provide a minimum of 10 consecutive cases diagnosed during the period 2010-2015 per tumour** (i.e. at least 10 neuroblastoma and 10 Wilms tumour cases), if their number of cases per year is less than 10, and that **larger registries provide cases from 1 calendar year of incidence** during the same period**.** Only 11 countries in Table 1 collect the required number of cases in a year (Austria, Belgium, France, Germany, Hungary, Italy, Spain, Sweden, Switzerland, the Netherlands, England & Wales). For the other registries two or more years are then required. Cases have to be all those **consecutive in the indicated time period** chosen by the registry after completing the incidence data collection for that time period. Cases with problem with the definition of stage because of scarcity of information **must** be included and **not** eliminated. Cases where the neuroblastoma or Wilms tumour are a second tumour in the same child should be included and it should be noted that the case is a second tumour.

Each record (case) includes demographic variables as those of the EUROCARE/RARECAREnet projects plus the information of examinations used by the registrars for staging and confirmation that the defined stage is assigned according to the Toronto consensus guidelines (see **structure of the record**, Table 2). Also, it is important to collect the information on the data sources used for defining stage (clinical record, administrative, pathological reports, others).

Where cases of neuroblastoma and Wilms tumours have **already been staged**, registries should either confirm that this was done according to the Toronto staging guidelines. If not, we ask them to **restage** their cases according to the Toronto rules.

We will also use this initiative to test how much information registries currently hold on **disease recurrence** and progression. This request for collecting recurrence and site of recurrence is optional data. Registries are asked whether it is possible for them to collect this item on the 10 cases/one year's worth of cases at the same time as enhancing the staging data of each case and whether the same methods would be needed to do this.

Oversight of the project

Day to day management of the project will be performed jointly by Dr Gemma Gatta, INT, Milan and Prof Kathy Pritchard-Jones (paediatric oncologist, University College London, UK).

All participating registries will be members of the overall Working Group and will receive regular updates on the project's progress, and will be co-authors on any publications resulting from this work. Colleagues who led the development of the Toronto consensus staging guidelines (Dr Sumit Gupta, POGO, Toronto, and Dr Lindsay Frazier, Boston, USA) together with Dr 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 implementation in Australia, have kindly offered to join the group as advisors [7]. They have already developed business rules that they are happy to share with us and welcome our input into their further iteration as they are applied more widely.

Table 2: structure of the record

Field	Variable	No. of characters	Notes and encoding
1-10	Basic variables		
1	Registry	10	alphabetic
2	Registry Patient Identification code	10	
3	Date of birth	10	dd/mm/yyyy
4	Age	3	numeric
5	Date of diagnosis	10	dd/mm/yyyy
6	Sex	1	1=boy; 2=girl
7	ICDO3-Topography	3	Only the numeric part of the ICD-O-3 topography code will be reported (the "C" and "." will not be included)
8	ICDO-3-Morphology	4	Malignant, only, behaviour code=3
9	Multiple tumour	1	Y/N/unknown 1/0/9
10-15	Imaging for staging		
10	CT	1	Y/N 1/0
11	MRI	1	Y/N 1/0
12	Abdominal ultrasound	1	Y/N 1/0
13	Scintigraphy	1	Y/N 1/0
14	Agobiopsy marrow	1	Y/N 1/0
15	x-ray thorax	1	Y/N 1/0
16-18	Toronto staging, Neuroblastoma		
16	Stage Tier 1	2	L/LR/M/MS/X
17	Stage Tier 2	2	L1/L2/M/MS/X
18	Laterality	1	R/L/B 1/2/3
19-25	Toronto staging, Wilms tumour		
19	Postchemotherapy Stage Tier 1	1	L/M/X
20	Postchemotherapy Stage Tier 2	1	1/2/3/4/X
21	Prechemotherapy Stage Tier 1	1	L/M/X
22	Prechemotherapy Stage Tier 2	1	y1/y2/y3/4/X
23	Imaging performed for metastases before surgery	1	Y/N 1/0
24	Thorax x-ray performed for metastases before surgery	1	Y/N 1/0
26	Laterality	1	R/L/B 1/2/3
27-33	Source of the examination for staging		
27	Clinical report	1	Y/N 1/0
28	Pathological report	1	Y/N 1/0
29	Administrative files (hospital discharge, etc.)	1	Y/N 1/0
30	Autopsy	1	Y/N 1/0
31	Death certificate	1	Y/N 1/0
32	Others	1	Y/N 1/0
33	Others (string)	10	alphabetic
34-39	Other variables		
34	Relapse	1	Y/N/unknown 1/0//9
35	Site of relapse	10	alphabetic
36	Date of relapse	10	dd/mm/yyyy
37	Chemotherapy drugs given	1	Y/N/unknown 1/0/9
38	Drug names	10	alphabetic
39	Radiotherapy given	1	Y/N/unknown 1/0/9
40	Radiotherapy fields if given	10	alphabetic
41-42	Follow-up		

41	Status of life alive/dead	1	alive/dead 1/2
42	Date of last contact or dead	10	dd/mm/yyyy

Confidentiality: Any requirement for ethical or regulatory approval to collect data and the format in which it can be shared should be dealt with at a national or regional level. This document should be used as the final protocol describing the work to be undertaken to assess the feasibility of applying the Toronto staging guidelines by European cancer registries with population based cancer registry data.

Data collection: After the approval of the protocol from the participating registries and the expert partners involved in the study, we expect to collect the information in a month. We would like to receive at least 20 cases per registry, 10 per type of tumour for small registries and one year of cases for large registries. However, a **more precise Table 1** will be provided after receiving from registries, detailed information of the period of incidence available for the study and the number of cases per year already collected and for which the definition of stage will be performed.

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

Meetings, data submission and timeline. Data will be centralised for data check and analysis at the INT, Milan, Italy. We expect to have the data from registries by the end of April 2018. A first meeting by teleconference was held with registries on 25 October 2017, to discuss the protocol and any anticipated problems with data definitions or collection, leading to the refinement of the protocol to this version 6. We will have a face to face meeting for the presentation of the results with a date to be agreed in the summer of 2018.

Deliverables and other questions.
This pilot feasibility study will provide recommendations for collecting staging in cancer registries for the JARC, WP4, deliverables - improve quality of data registration and model to evaluate impact of ERNs - and contribute to the milestone report on status of eHealth – medical record development in European countries (including privacy and security measures), JARC WP7, task 7.2.

Recommendations have to identify the major challenges in collecting paediatric cancer stage and the solutions to overcome these. Sources of data are different according to the different organization of registries and their size. The impact on completeness and quality of stage using different sources will be considered. **Resources needed to collect valid paediatric stage data across various resource setting have to be identified and measured**.

Planned next steps after completion of the pilot study
After completion of this pilot study, we will understand the capability of each country's population-based cancer registration system to collect tumour staging data for two paediatric solid tumours and the resources and data sources required to achieve this. The planned next steps for those interested cancer registries and associated clinical registries/trial groups is to identify potential sources of grant funding and to submit a joint application to undertake a definitive study on outcomes by tumour stage.

References

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Appendix

Neuroblastoma list of vital structures

Neck

- Tumor encasing carotid and/or vertebral artery and/or internal jugular vein
- Tumor extending to base of skull
- Tumor compressing the trachea

Cervico-thoracic junction

- Tumor encasing brachial plexus roots
- Tumor encasing subclavian vessels and/or vertebral and/or carotid artery
- Tumor compressing the trachea

Thorax

- Tumor encasing the aorta and/or major branches
- Tumor compressing the trachea and/or principal bronchi
- Lower mediastinal tumor, infiltrating the costo-vertebral junction
- between T9 and T12

Thoraco-abdominal

- Tumor encasing the aorta and/or vena cava

Abdomen/pelvis

- Tumor infiltrating the porta hepatis and/or the hepatoduodenal ligament
- Tumor encasing branches of the superior mesenteric artery at themesenteric root
- Tumor encasing the origin of the coeliac axis, and/or of the superior mesenteric artery
- Tumor invading one or both renal pedicles
- Tumor encasing the aorta and/or vena cava
- Tumor encasing the iliac vessels
- Pelvic tumor crossing the sciatic notch

Intraspinal tumor 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

Conditions to be recorded, but not considered IDRFs (image-defined risk factors)

- Multifocal primary tumors
- Pleural effusion, with or without malignant cells
- Ascites, with or without malignant cells