Supplementary material for "Brain cancer after radiation exposure from computed tomography examinations among children and young adults: results from the EPI-CT cohort study" (Hauptmann et al)

Table S1: Brain cancer diagnostic categories by morphology

Brain malignancy category*	Morphology code	Number
Overall		165
Glial, astrocytic and ependymal**	9380-9382, 9391, 9392, 9393, 9400, 9401, 9410, 9411, 9420, 9423-9425, 9430, 9440-9442, 9450, 9451, 9460	121
Meningioma	9530, 9538, 9539	5
Embryonal	9364, 9470-9474, 9480, 9490, 9500, 9501, 9571	14
Other	8272, 8680, 8728, 9064, 9362, 9505	9
Not otherwise specified	8000	16

* ICD-O-3 topography site codes C70.0, C70.9, C71.0-C71.9, C72.2-C72.5, C72.8, C72.9, C75.1, C75.3 for all subtypes except for meningioma, which are restricted to C70.0-C70.9

** Referred to as glioma in the manuscript

Table S2: Country-specific sensitivity analyses of linear excess relative risk per 100 mGy brain dose (lagged by 5 years, 5-year exclusion period)

	All brain cancers		Glioma	
	Number of cases included	ERR/100 mGy (95% CI)	Number of cases included	ERR/100 mGy (95% CI)
Included countries				
All countries	165	1·27 (0·51, 2·69)	121	1·11 (0·36, 2·59)
Belgium, Denmark, France, Germany, Norway, Spain	0+1+3+1+9+0	3·09 (0·03, 82·82)	0+1+2+0+8+0	2·82 (<-0·01, 89·45)
Netherlands	29	0·82 (-0·09, 4·50)	19	0·80 (-0·13, 5·03)
Sweden	28	0·38 (<0, 3·17)	21	0·08 (<-0·15, 2·36)
UK	94	1·65 (0·50, 4·58)	70	1·67 (0·41, 5·41)
LSS*	Not reported	0·61 (0·01, 6·39)		
Left-out country**				
None	165	1·27 (0·51, 2·69)	121	1·11 (0·36, 2·59)
France	162	1.28 (0·52, 2·72)	119	1·11 (0·37, 2·61)
Denmark	164	1·18 (0·46, 2·55)	120	1·00 (0·30, 2·42)
Germany	164	1·29 (0·52, 2·73)	121	1·11 (0·36, 2·59)
Netherlands	136	1·41 (0·52, 3·23)	102	1·20 (0·35, 3·10)
Norway	156	1·20 (0·46, 2·61)	113	1·12 (0·36, 2·66)
Sweden	137	1·53 (0·59, 3·48)	100	1·47 (0·48, 3·70)
UK	71	0·91 (0·12, 2·83)	51	0·65 (-0·03, 2·45)

ERR, excess relative risk; CI, confidence interval; LSS, Life Span Study

* The original Life Span Study population was restricted to subjects with age at exposure<20 years and follow-up duration<20 years after exposure, calculated by Pearce *et al*[9]

** Belgium and Spain did not contribute cases

Table S3: Relative risks by cumulative brain dose (lagged by 10 years, 5-year exclusion period)

Cumulative brain dose (mGy)	All brain cancers		Glioma	
	Cases	RR* (95% CI)	Cases	RR* (95% CI)
0-<5	99	1·0 (ref)	69	1·0 (ref)
5-<41	14	1·1 (0·6, 2·1)	11	1·2 (0·6, 2·4)
41-<48	13	1·5 (0·8, 2·8)	12	1·9 (1·0, 3·7)
48-<56	13	1·0 (0·5, 1·8)	9	0·9 (0·4, 1·9)
56-<65	11	1·2 (0·6, 2·4)	7	1·1 (0·5, 2·4)
65-<150	12	1·1 (0·6, 2·1)	10	1·3 (0·7, 2·6)
150+	3	1·2 (0·4, 3·8)	3	1·7 (0·5, 5·4)
ERR/100 mGy (95% CI)	0·19 (<-0·20, 0·79)**		0.34 (<-0·17, 1·13)**	
P***	0·35		0·18	

CI, confidence interval; RR, relative risk; ERR, excess relative risk

* Poisson regression stratified for calendar year, attained age, gender and country

** No evidence of non-linearity, p>.1

*** P-value of coefficient for continuous dose in linear model

Table S4: Results of sensitivity analyses for all brain cancers with respect to outlying brain doses and CT examinations performed before 1990 (5-year exclusion period, 5-year lag)

Sensitivity modifications	Cases	ERR/100 mGy (95% CI)
Excluded from analysis		
1% person-years with highest brain doses (>333 mGy)	161	1·45 (0·57, 3·13)
2% person-years with highest brain doses (>260 mGy)	153	1·06 (0·23, 2·62)
3% person-years with highest brain doses (>175 mGy)	149	0·94 (0·09, 2·54)
Person-years with ≥2 head CT examinations	126	1·17 (0·02, 3·33)
Subjects with first CT before 1990	133	1·41 (0·51, 3·30)
Maximum brain dose included in analysis (mGy)		
40	45	1·77 (-0·58, 6·45)
50	71	2·38 (0·34, 6·34)
60	113	1·41 (0·09, 3·92)
70	121	1·50 (0·17, 4·00)
80	130	1·31 (0·12, 3·59)
90	130	1·16 (0·03, 3·31)
100	135	0·82 (-0·11, 2·56)
120	147	1·00 (0·10, 2·70)
Exclusion period (years)		
5*	165	1·27 (0·51, 2·69)
6	145	0·99 (0·33, 2·27)
7	122	0·81 (0·20, 2·05)
8	99	0·76 (0·15, 2·07)
9	86	0·51 (0·07, 1·69)
10	76	0·37 (-0·06, 1·40)
Maximum attained age (years) included in analysis		
20	78	1·49 (0·39, 4·67)
25	116	2·16 (0·79, 5·65)
30	142	1·92 (0·79, 4·36)
35	156	1·51 (0·63, 3·24)
40	164	1·28 (0·52, 2·71)
Minimum calendar year included in analysis		
1995	154	1·00 (0·35, 2·22)
2000	142	1·10 (0·38, 5·54)
2005	106	0·95 (0·26, 2·36)
2010	62	1·32 (0·27, 4·40)
Minimum birth year included in analysis		
1980	119	1·22 (0·40, 3·04)
1990	154	2·67 (0·51, 17·90)
1995	19	6·22 (0·22, 122·00)

ERR, excess relative risk; CI, confidence interval

* Primary analysis

Table S5: Relative risks for all brain cancers excluding glioma by categories of cumulative brain dose (5-year exclusion period, 5-year lag)

	All brain cancers excluding glioma	
	Cases	RR* (95% CI)
Cumulative brain dose (mGy)		
0-<5	2	1·0 (ref)
5-<41	9	4·3 (0·9, 19·8)
41-<48	5	3·5 (0·7, 17·9)
48-<56	6	2·7 (0·5, 13·6)
56-<65	9	6·2 (1·3, 29·4)
65-<150	8	4·6 (1·0, 21·8)
150+	5	11·9 (2·3, 62·1)
p value**	0·0085	
ERR/100 mGy[$] (95% CI)	2·13 (0·25, 13·6)	

RR, relative risk; CI, confidence interval; ERR, excess relative risk

* Poisson regression stratified for calendar year, attained age, gender and country

** P-value of coefficient for continuous dose in linear model

[$] No evidence of non-linearity, p=0·26

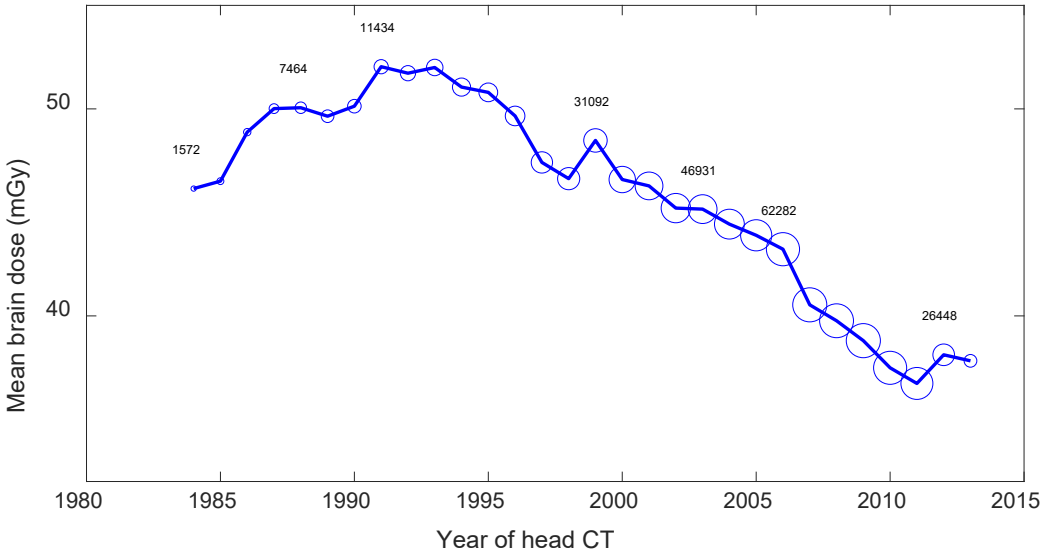
Table S6: Modification of radiation-related risk for all brain cancers excluding glioma (5-year exclusion period, 5-year lag)

	All brain cancers excluding glioma	
	ERR/100 mGy (95% CI)	P hom
Sex		
Male	3·28 (<-0·27, 56·67)	
Female	0·79 (<-0·70, 21·01)	0·44
Age at CT exposure (years)		
0-<6	1·41 (<-1·33, 13·32)	
6-<12	3·99 (<-0·22, 26·43)	
12+	1·99 (<-0·38, 15·66)	0·66
Attained age (years)		
5-<18	40·09 (<-0·83, >403·90)	
18-<25	0·73 (<-0·98, 13·93)	
25+	1·80 (<-1·65, 49·64)	0·40

ERR, excess relative risk; CI, confidence interval; hom, homogeneity; NA, not available

The model for time since exposure did not converge

Figure S1: Mean brain dose from head/neck CT examinations by year of CT examination (diameter of circles proportional to number of head/neck CT examinations, which is provided for selected years). Data prior to 1984 are not shown due to the small number of CT examinations.



International Collaborative Study: EPI-CT

Epidemiological study to quantify risks for paediatric computerized tomography and to optimise doses

PROCEDURES DOCUMENT

Version 6

This document complements the study protocol and presents the standard procedures agreed upon by the Work Beneficiaries of the Study for the conduct of the study. The principles underlying these procedures are outlined, as well as the specific procedures adopted in each country.

Project acronym EPI-CT
Project full title “Epidemiological study to quantify risks for pediatric computerized tomography and to optimise doses”.
Grant agreement nº of project 269912

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

CAATS Centre d'Assurance de qualité des Applications Technologiques dans le domaine de la Santé, France
CREAL Centre for Research in Environmental Epidemiology, Spain
CRP Centre de Recherche Public Henri Tudor, Luxembourg
DCS Danish Cancer Society, Denmark
IARC International Agency for Research on Cancer, Lyon, France
IC Institut Curie, France
IGR Institut Gustave Roussy, France
INSERM Institut National de la Sante et de la Recherche Medicale, France
IRSN Institut de Radioprotection et de Surete Nucleaire, France
KI Karolinska Institute, Sweden
NKI Netherlands Cancer Institute, the Netherlands
NRPA Norwegian Radiation Protection Agency, Norway
OUS-CRN Oslo Universitetssykehus, Norway
SCK•CEN Belgian Nuclear Research Centre, Belgium
STUK Radiation and Nuclear Safety Authority, Finland
UGent Universiteit Gent, Belgium
UMC Universitaetsmedizin Der Johannes Gutenberg-Universitaet Mainz, Germany
UNEW Newcastle University, United Kingdom

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1. OBJECTIVES OF THE STUDY

A. BACKGROUND

Diagnostic radiation represents an indispensable, sometimes life-saving, tool in modern medicine. The growing use of diagnostic high-dose techniques (CT, interventional procedures using X-rays) in children and adolescents (1-4) is a topic of concern, however, in radiological protection and public health (5-9), as studies of atomic bomb survivors and other populations with medical and environmental exposures indicate that children have higher relative risks of radiation induced disease per unit dose of radiation than adults (9;10). In addition, children have a longer life span to develop any radiation-related health effect and, because of their smaller mass, children tend to receive higher doses to specific organs from these procedures than do adults unless settings are adjusted for paediatric patients.

In children, doses to target organs can be of the order of a few tens of mGy and cumulative doses may reach 100 – 200 mGy if examinations are repeated (7;8). The epidemiological information regarding radiation health effects of early childhood exposures to low doses of ionizing radiation remains limited, particularly by the lack of information on early childhood cancers in the years immediately after the atomic bombings in Japan.

In 2008-09, under EU Grant agreement FP7-212839, CHILD-MED-RAD project was conducted to assess the feasibility of establishing prospective trans-national European cohorts of paediatric patients with substantial diagnostic radiation doses, suitable for long-term follow-up. Issues of exposure assessment were assessed for contemporary medical records, as well as for historical records, which may include less detailed information regarding how the procedures were conducted. The project demonstrated the feasibility of an international cohort study of paediatric CT procedures and in 2010 EPI-CT was set up. EPI-CT aims to bring together the national studies already ongoing in Europe (UK, Germany and France) and to set-up additional studies in six other countries (Belgium, Denmark, the Netherlands, Norway, Spain and Sweden).The current document describes the detailed procedures of the study.

B. OBJECTIVES

The primary objective of the EPI-CT study is to estimate directly, and as precisely as possible, the health consequences of radiation exposure from CT scans in childhood and adolescence.

The specific purpose of the study is to establish a transnational cohort of paediatric patients who received CT scans for long-term follow-up. This will allow us evaluate the radiation related risk of leukaemia and all cancers combined as outcome. Secondary analyses will focus on specific tumour types for which there are enough cases/deaths, such as cancers of the brain. A first evaluation could be conducted in the first 5 years of the project, though further follow-up of the population would be crucial to increase the precision of risk estimates. Also, the influence of age at exposure as a modifier of individual susceptibility to radiation-induced cancer will be investigated.

The study is aimed also to describe the patterns of use of CT scans over time and among countries. In addition, recommendations on how to reduce risk keeping image quality will be generated from working with manufactures and provided to the radiology personnel involved in medical imaging obtaining.

2. CONSTRUCTION OF COHORTS

A. PRINCIPLES

1. Study population

Within each country, the study population that will constitute the national cohort is defined on the basis of records of radiology departments within participating hospitals. Efforts will be made to include all large hospitals in the study regions that serve paediatric patients.
The study population for each country/cohort is given below, in the country-specific procedures section.

2. Study subjects

Eligible subjects are all patients with an indication of at least one CT scan who were less than 15 years of age at the time of the procedure. In several of the participating countries, patients will also be included who were 15-18 or 15-20 years of age at the time of the CT scan procedure (see country-specific procedures section). The preferable range age may vary among the countries depending on the coverage of the existing registry. Patients will be excluded if they are non-residents of the country.

3. Study design and study period

The study includes, depending on the country and availability of funds, either only a retrospective cohort design with prospective follow-up or a combination of **retrospective and prospective cohort studies**, with continued accrual of subjects and updating of exposure over a number of years. Follow-up of all cohorts will be conducted at least through 2011. In most countries, accrual and updating will not be done in real time but at periodic intervals (1 to 3 years).

In some countries (UK, Germany and France) retrospective cohorts have already been set up and in UK the period of scan data will be extended to include more recently exposed children.

Retrospective cohorts will allow us to derive risk estimates in the short term and provide quantitative results within the first five years of the proposed study. However, it is unlikely that we can establish retrospective cohorts that are large enough to derive highly precise statistical estimates. Furthermore, information for dose reconstruction is poor in earlier years relative to the quality of information in more recent years. Therefore the study protocol will support expansion of the existing cohorts to continue to accrue paediatric patients who received CT scans in more recent years.

Prospective collection of information on CT scans will allow for detailed dose reconstructions as well as expansion of the study cohort. This also will serve as a surveillance tool to monitor changes in exposures associated with these rapidly evolving technologies. While epidemiological findings based upon patients that have been enrolled prospectively in this trans-national study will not be available for some time, they may be helpful in better quantifying risks as it is expected that more detailed dose estimation will be possible. In 2015 we plan to have the first analyses point. If funding is found the follow up of the European cohort will continue for the years to come.

4. Overlap of cohorts

Patients who have received a CT scan in different participating hospitals in the same country will be identified in each hospital and the information will be linked in the national database so that their exposure history can be reconstructed appropriately (see section on personal identifiers below).

If subjects have received CTs in different participating countries, it will not be possible, due to data protection laws, to exchange identifying information and hence to identify them.

B. COUNTRY SPECIFIC PROCEDURES

1. Summary table

Table 1. Characteristics of country specific cohorts

Country / Cohort	Study population	Age (yrs)	Start of the cohort accrual and follow-up period	Planned period of cohort accrual (years)		Actual cohort Size	Expected cohort Size
				Retrospective (up to 2010)	Prospective 1st phase (up to		
EU							
Belgium	Paediatric patients from participating hospitals	0-15	2002	9	4	-	30,000
Denmark	Paediatric patients from participating hospitals	0-18	2000	11	4	-	30,000
France	Paediatric patients from participating hospitals	0-5	2000	11	4	40,000	90,000
Germany	Paediatric patients from participating hospitals	0-15	1985	30	4	10,000	140,000
Netherlands	Paediatric patients from participating hospitals	0-18	1998	13	4	-	40,000
Spain	Paediatric patients from participating hospitals	0-15 (or 0-18)	2005	6	4	1,000	200,000
Sweden	Paediatric patients from participating hospitals	0-18	1984	27	4	-	95,000
UK	All that can participate	0-21	1985	26	4	250,000	150,000*
Non-EU							
Norway	All that can participate	0-20	2005	5	4	-	20,000

* included only in the current proposal

2. Particularities

Belgium

Two large hospitals in Flanders agreed to participate in the study; one university hospital and one large general hospital. A cohort of about 30.000 children from 0-15 years of age will be recruited during the period from 2002 and 2011. The implementation of PACS in the participating hospitals is done around 2000-2002. However, in one of the hospitals, the identification of numbering of patients has changed in 2006 which means that the data extracted from RIS to query the PACS before 2006 could give much more examinations than just the requested CT examinations. The RIS list should be checked manually, for which permission still needs to be obtained. Therefore, depending on the hospital, data collection might start in 2000 or 2006. Belgium will use its own software to extract the data from PACS.

Denmark
Paediatric patients (below 18 years at the time of examination) are scanned in four major clinics performing the vast majority of all scheduled scans in children (Copenhagen, Arhus, Aalborg, Odense), out of a total of 31 units. Young adults can also be included in the cohort.

France
Inclusion of children limited to those born after 1994 in order to be able to check manually the possible occurrence of cancer before 2000 in the study population. Until now, the registry follow-up was limited to 15 years of age, so it was decided not to include children older than 10 years because of the lack of follow-up, even with the future possibility of extending the cancer registry to young adults of maximum 20 years old.

Germany
The patients included range from 0-15 years old at the time of CT examination. All patients will be followed for cancer incidence until 15 years old by pseudonymous record linkage with the German Childhood Cancer Registry. In the prospective study, the follow up till age of 18 is likely. There will be some children who will be followed only few months.

The Netherlands
The study population is defined as children below 18 years of age at the time of the first CT examination in one of the 8 academic hospitals between 1999 and 2012. The first year of inclusion vary by hospital, depending on the introduction of electronic archiving of CT scans. The estimated size of the cohort is approximately 40,000.

Spain
In Spain, information on children from 0 to 20 years of age at the time of the first CT examination is collected in three different regions (additional funding has been obtained to expand the project from the 2 regions covered by the EU funds to a third one) that are covered by regional cancer registries (there is no a centralised unique cancer registry for the whole country. Other regions may be evaluated to take part on the project depending on information quality and additional funding. Cancer registries in participating regions are well established; most having contributed data to Cancer Incidence in V Continents and a number of them have been used in the follow-up of cohorts. The only new cancer registry is that of Cataluña, which has been under construction over the last 5 years and is about to be completed. The full cancer registry should start within 1-2 years and will be a very good tool for prospective follow-up, with coverage of about 7 million persons.

Sweden
Six major groups of hospitals agreed to participate (four university hospitals and two counties with complete coverage), including 95,000 patients scanned from 1984 onwards.

United Kingdom
The patients included range from 0-21 years old.
In the UK study all cohort members are permanent flagged in national mortality database and new outcomes are identified on a continuous basis.

Norway
Norway cohort aims to include all public hospitals, but first year of inclusion is estimated to vary from 1995 to 2003 in the different hospitals/regions. Subjects aged below 20 years who have had one or more CT scans at a Norwegian hospital after the introduction of RIS will be included in the cohort.

3. DATA COLLECTION

A. PRINCIPLES

The protocol of the study describes the desirable minimum set of variables which should be collected in principle for all cohort members. These variables concern personal identifiers, technical features of the scan examination and also, reason and hospital ward referral. Data of interest is specified also in the protocol and compiled in a table below.

Height and weight at the time of scan should be recorded, and if it is not available in the radiology records (quite unlikely in RIS files), attempts should be made to obtain the information by linkage with other hospital records where possible and information available. In the later case, the date when weight and height were obtained should be specified. If not available, height and weight distributions for the respective country and period and age should be used to provide average value and confidence interval.

During data collection, it will happen that information needed for accurate dosimetry will not be available A variable which may not be available in the RIS or PACS is the shielding protective equipment used – this will be very important for dose reconstruction accuracy (7). The most efficient option to record this would be to modify one of the empty labels at the DICOM header and to assign a value defining the use of shielding protective equipment. A common code system to be used is suggested at the end of this section (see table 3). Obviously, it will be possible only for the prospective part of the study and needs that the technicians enter the information for each examination.

A list of manufacturers and scanner models used in the participating hospitals has to be provided to NCI for dose reconstruction. Even though DICOM headers contain two labels regarding manufacturer and manufacturer's model name it will be helpful to send all the information to NCI as soon as possible, not once the data extraction in each participating hospital has been done. Henri Tudor Research Group will need information regarding the settings of the machine, so record the manufacturers' software used for managing the images at each participating hospital (see annex 1).

IARC is responsible for developing a common structure for a database and for its distribution to all partners for management of collected data. Draft versions of the database will be tested so that it can be optimised and finalised. At the moment of the current version of procedures document it is not decided if EPI-CT project will have assigned a centralised physical database, or a virtual international database for the whole cohort.

If the database is centralised, this means that the countries will need to send updated copies of the entire database to the central database for extraction of the analysis files to be sent out to the centre in charge of analysis. If the database is virtual, then, at the time of analysis, each country will need to run a common query, provided by the international database manager, to extract the analysis file based on the most up to date data and send it to the centre in charge of data analysis.
Every country will need to maintain and update their national database and the European database manager will be available to assist with this.

1. Identifying information

Identifying information, necessary for linking all data on an individual, must be collected at the national level but must not be sent outside of the country. The main database (either if it's

centralised or if each country keeps its own one) will include a procedure for removing identifying information when the data need to be exported.

A unique within country identifying number will be assigned to each cohort participant but this should not be any number, such as social security or health insurance number, which could allow the identification of a subject outside the study. The unique identifying number will follow the identification system suggested below:

Country code [1] – **Hospital code** [2] - **Sequencing number within the hospital**
(2 digits) where it was recruited (3 digits) in order of accrual (5 digits)

[1] Country code
(to be followed by participant countries)

[2] Hospital code:
(each country sets up its own hospital codes)

Country/cohort	#
Belgium	01
Denmark	02
France	03
Germany	04
Netherlands	05
Norway	06
Spain	07
Sweden	08
UK	09

Hospital (examples)	#
Hospital Sant Joan de Déu	001
Hospital Vall d'Hebron	002

Examples:

Participant	Assigned code
A	0500200001
B	0700200784
C	0700100035
…	

Country / cohort	Hospital	Participant #
Netherlands	Erasmus Medisch Centrum	00001
Spain	Hospital Vall d'Hebron	00784
Spain	Hospital Sant Joan de Déu	00035

It will need the creation within each country of a protected key code that allows the linkage of the full identifying data for further follow-up and to the data specified below, in a way which protects the personal information and which is accepted by the appropriate privacy protection authority, where relevant.

ONLY codes have to be sent outside of the study country to avoid the potential identification of hospitals.

The personal identifiers necessary for linkage between different sources of information - to ensure correct match of information on exposure, mortality and morbidity may differ between countries. Identifying information which may be useful for linkage includes, for example, names (family, first, middle, maiden), date and place of birth, last address and the date this address was obtained, and national identifying numbers (Social Security, National Health Service, National Identity document, etc.).

Because inaccuracies in recording personal identifiers are often encountered, availability of additional individual identifiers will greatly increase the success of linkage between records. The identifiers collected for linkage from each source of information (exposure, outcome, death, etc.) are listed below by country/cohort; and will not be sent out to the country.

Each country has to establish how they will identify patients to be excluded because of cancer at the time of their initial CT scan. For more details, see section 5. A1 'Confounding by indication'.

2. Initiating data collection

This phase will start when the research teams leading EPI-CT in a specific country count with full support from the Paediatric Radiology department of the participating hospital. When approaching a hospital looking for its participation the head of the radiology department may be the person to put you in contact with some professionals of his/her team that may be willing to participate in the study. From the experiences in UK and Germany we learned that it's advisable to involve the IT personnel of the respective hospital as early as possible to ease and speed the abstraction process. The combination of a variety of contacting methods to inform radiologist about EPI-CT study (calls, e-mails and visits) helps to ensure data from as much hospitals as possible, as experienced in UK. According to the experience in Spain, the first approach consists on a first call to the hospital and a brief introduction to the project with the Head of Radiology Department. Once his/her email address is obtained additional information (core protocol and a 2 page-summary of the project) is sent by email. Once we receive their interest in participating on the project, personal meetings follow. According to the experience of France, the contact of the national paediatric radiology society is very helpful.

Also data collection will need the protocol approval by the Ethics Committee of the participating hospital or other national authority. All Ethic Forms used for obtaining the protocol approval by the Ethics Committee (Patient Informed Consent Form, Poster informing on EPI-CT study, etc.) and the Protocol Approval form from each Ethic Committee within a country have to be submitted to IARC. At the same time all participating countries can get help from the IARC Review board and the Ethics Committee created at the Kick-off Meeting (see list of EPI-CT Committees and working groups at the beginning of this document). Ethics Committee approval is supposed to be obtained by February 2012.

Data collection commences by enumeration of a roster of patients who underwent CT scans in a particular hospital, fall into the age range of 0-20 years old at the time of their first CT scan (0-15, 0-18 depending on the country and are res) and are residents on the country.
Data collection period can be split into two, the first before the introduction of PACS, the second after the introduction of PACS. See country specific procedures section for specific kind of records available in each country.

2.1 Collection of data from RIS and other radiology records pre-PACS

Newcastle University coordinates RIS data extraction.

Once the collaboration of the Radiology department is granted, it is important to pass to the RIS administrator information on the variables we want to extract from the system, in advance. These parameters and the complementary ones from other medical records are listed below, at the table 2.

Data from RIS will be downloadable directly from most radiology departments in participating hospitals. Following data extraction we will obtain one or several files that we will merge into an only one file, preferably a tab delimited text file, but always adapted to the particularities of the hospital.

A study ID will be assigned to each participant using as in Germany distinct random numbers leaded by the hospital ID or, as in other countries, in order of accrual as described in the previous 'Identifying information' section. The assigned study ID should not allow the identification of a subject outside the study. A key linking personal data (name, birth date, sex) with the assigned study ID will be created and kept at the research centre in a safe server with restricted access to the researchers in charge of the study. The operating database will not contain personal data (National Identification number, name and surnames); only data of birth and home postal code will be kept for the analyses.

At the research centre, all work on sensitive data will be performed following strict measures ensuring data protection, and only data with a study ID will be transferred to any other database out of the research institute, in specific circumstances such as for the definition of the international cohort and further analyses. The transfer of these data from the participating hospital to the research institution will be executed using a password protected hard drive.

The data flow and data protection strategies may vary by country due to country specific regulations and are indicated below.

In a small number of cases paper or film records may also be available and abstracted to obtain data of interest.

2.2 Collection of data from PACS

UMC & Henri Tudor Research Group are the coordinators of PACS data extraction. Main rule for data extraction using PACS is not to interfere in the daily routine of the radiological service.
Data extraction will start with the creation of the patient's roster. The roster will be a .txt file containing the patient IDs (one per line) as they appear in the medical records and its accessibility will be restricted to the participating researchers and the close medical team of that particular hospital involved in EPI-CT study. It is possible to obtain the patients' roster from RIS or from any other system of managing radiologic data.

For the automatic extraction of data from individual images within PACS system, the software PerMoS needs to be run on a computer at the participating hospital. The minimum requirements for this computer are:

- Support Java 1.6
- 2 Gb RAM memory
- Internet connection for downloading PerMoS software and uploading of data, if needed.
- Connected to the server where PACS is connected to generate queries as a client.
- Free space (roughly more than 1 GB per 200 patients) to store stripped files.

Regarding the computer, different options may work according to the available hardware at the hospital and the distribution of the study budget in each country. An option would involve the purchase of one/several computers to automatically extract the radiologic data from one hospital/several hospitals and once the task is completed, the computer/computers could be installed in the following hospitals for data extraction. Another option would mean to work with the computers available at the Hospital. In any of the 2 cases the best approach means involving the IT department of the hospital in order to have its support and acceptance. The procedures regarding installation, use and particularities of the software are described in the

'PerMoS configuration sheet' and 'PerMoS Manual' that you can download as an EPI-CT member from the following website: http://santec.tudor.lu/project/epict/members/start&?do=login

For the connection, setting and testing of the software, from 30 minutes to 2 hours may be required. PerMoS will allow us to query your PACS system for images by providing a list of patient IDs from a file and this software does not write or introduce data on PACS, as said, it just works as a client producing queries.

So, we will proceed to download the software from PerMoS website and to install it at the computer selected for data querying. First of all you need to configure the DICOM Receiver Tab. If the DICOM Receiver is configured and working you need to configure the query functionality in the settings dialog.

It is necessary to set the time and frequency at which these queries will be produced. Since queries of data from PerMoS to PACSs means moving heavy loads of data through the system, queries should be scheduled for periods of low density of server queries, for example, during the week late at night and on the weekends starting a little bit earlier. In Germany, queries were scheduled from 6 pm to 7 am and at the frequency of a query each 60-120 seconds but both parameters should be adapted according to the specific reality of each radiology department. The query time will add around 5 minutes per query so the total amount of time needed for 1 query fluctuates from 2 to 7 minutes.

- Query interval: Interval in which the queries are fired to the PACS in seconds
- Starting time: starting hour of the timed query function. This allows you to only query retrieve during the night when the PACS is bored.
- Ending time: ending hour of the timed query function.

To start the query you need to select the file containing the patient IDs by using the select folder button. Queries may not be generated logically (like 'Birth-Exam<=15 AND Examination=CT'), thus the potential cohort has to be listed in a text file (.txt) beforehand by ID (one per line), obtaining this information from RIS.
After that you can either start the Query/Retrieve by using the Start/Stop button or use the Timed Query/Retrieve button to only request to the PACS during the configured hours. A progress and log of the Upload will be displayed in the left area of the tab.
You need also to configure the DICOM receiver tab in the settings dialog. The following settings need to be made:

- Receiver AE Title: The AE title with which this DICOM node is registered in the sending Modality/PACS
- Receiver Network Port: The port on which this receiver is listening.
- Receiver IP Address: The IP address of the local DICOM-STORE is shown for information purposes but can not be changed.

To make the Query/Retrieve work you need to configure a DICOM Node in your PACS with the IP, Port and AET configured in the DICOM Receiver Tab.

The limiting factors in terms of speed of data extraction are the power of PACS, the available time for extraction and the network backbone. According to the German experience they extracted data from 150 patients per night.

Once the data is extracted each country may face different usage scenarios depending on the requirements of each hospital. We can:

- Upload the entire (relevant) PACS data from the hospital to a centralized database in Luxembourg using PerMoS;
- Like the first scenario, but the upload is not conducted from the hospital but from somewhere else;
- transfer the data to a national database, instead of the centralized database in Luxembourg using a secure File Transfer Protocol or whatever suits the hospital.

PerMoS data collector will return a list of scan protocol names (names assigned by each hospital to the different kinds of CT-scans) after the data transfer. They must be assigned to the calculation profiles by the radiology staff at the participating hospital, but according to the experience in Germany the elevated number of different scan protocols will not be make the assignation feasible.

In a second step will be decided which specific data will be extracted and used for the dose calculations.

NOTE I: Note: The original Luxembourg team proposal was to upload the PACS data to a server in Luxemburg for practical reasons. This may not be allowed in all hospitals thus the three different scenarios above.

In terms of patient identification, PerMoS will pseudonymise all PACS data by deleting all personal identifiers and overwriting the patient-ID with a hash-code. The file to link the pseudonym to the patients ID is generated automatically by PerMoS (but it needs to be manually saved in the computer) and will be kept inside the hospital. Additionally the algorithm to create the pseudonym is incorporated in PerMoS allowing encrypting an ID list without retrieving them from PACS.

Several concerns about PerMoS were raised at the EPI-CT kick-off meeting, such as the possibility to match patients across hospitals. One patient having a CT scan in two different participating hospitals will not be recognised since the algorithm will give that person different pseudonym in each hospital. However, whilst matching for the endpoint, the hospital specific cohorts can be matched too

A number of countries, however, need to keep the personal identification information (dissociated from the main database) to allow linkage to different data sources and may therefore not use the hash code converter.

NOTE II: A hash code generator can be provided by the German team. It's used by cancer registries and therefore reliable, even though it is not very handy. It can convert any information into hash codes, whereby names etc. will be converted based on their phonetics thus minimising mismatches due to spelling errors.

Table 2. Data desirable to obtain from RIS, PACs and complementary from other medical records

RIS	PACS
Patient identification necessary for linkage:	Patient identification necessary for linkage:
First name	First name
Last name	Last name
Sex	Sex
Date of birth	Date of birth
Address	Address
Hospital ID	Hospital ID
RIS ID	RIS ID
Other IDs (…)	Other IDs (…)
Name/code of radiology department	Name/code of radiology department
Date of scan	Date of scan
Scanner type	Scanner type
Body part scanned	Body part scanned
Number of scans	Number of scans
Use of contrast	Use of contrast
Reason for scan	Reason for scan
Hospital department from which patient is referred	Hospital department from which patient is referred
Height at the time of scan	Height at the time of scan
Weight at the time of scan	Weight at the time of scan
	Scan length
	Slice thickness
	Total collimation
	Scan increment
	Current
	Rotation time
	Voltage
	Pitch
	CTDI
	DLP
	Shielding equipment for protection

- CTDI and DPL are only set in recent scanners
- In old scanners, pitch, table feed and collimation might not be available
- For shielding equipment, there are two options – to ask the hospital IT department to modify a label of the DICOM that is not used or ask the hospital which kind of shielding equipment they use, for which scanner and which period
- Height and weight are usually unavailable in the DICOM header

Table 3. Shielding protective equipment desirable to be recorded in the radiology departments

Equipment	Code number
None	00
Bismuth Eye shield	01
Thyroid collar	02
Protective apron covering upper body + thyroids	03
Protective apron covering upper body up to sternum	04
Protective apron covering lower body, gonads included	05
Bismuth Breast Shield	06
Gonad shield	07
Half apron covering gonads	08

3. Management of data

The information from RIS, PACS, paper files and other systems will be merged into country-specific relational databases (database to be developed at IARC with input from all centres) to allow the identification of patients having repeated scans held under all recording modalities. At the same time is important to bear in mind that some hospitals will be using RIS alongside with PACS.

This will complete the construction of the initial cohorts for data linkage purposes.

NOTE: RIS holds the examinations, PACS the images of the examination; hence naturally there will be duplicates even though the information differs.

4. Compliance with study protocol in data acquisition

IRSN in collaboration with CREAL has developed a tool (data collection country specific progress report) to monitor that the study is on schedule in all participation countries. The report will be filled out by each EPI-CT participating cohort/country every 6 months from the start of data collection). IRSN will review the periodic progress report to identify delays, deviances from the study protocol and problems in the conduct of the study at the national level.

B. COUNTRY SPECIFIC PROCEDURES

Ethical issues

1. Description

As said, the starting point of the project in most of the countries will be to deal with the approval of the EPI-CT protocol by the competent authority, and both requirements and strategies to pass this step are country-specific.

2. Particularities

Belgium
To conduct a hospital based cohort study in children, approval from local ethical committees from each participating hospital (informed consent procedure, permission to access medical files, etc.), is required. Ethical approval is obtained in two hospitals so far, without the need of informed consent and only retrospective data collection is done. To obtain data, on an individual level, from the National Cancer Registry, approval from their scientific committee and permission from the national Privacy Protection Commission should be sought. The procedure has started.

Denmark
The study needs approval from the data protection board and National board of Health.

France
In France, passive information of subjects is required rather than written informed consent, through a poster displayed in the department of radiology. Individual consent was requested at the beginning by the ethics committee, but it took into account the difficulty of contacting thousands of people, since we did not collect complete postal address (only the postal code) in the study. It was accepted that a poster presents information about the project and gives participants the option to withdraw from the study if they wish. One radiology department gives the information poster to each child who is eligible for the study.

Germany
No need to request informed consent as the personal identification is replaced by pseudonyms that can be created from the personal data and used to link with the cancer registry. Information collected must however be destroyed after 10 years.

The Netherlands
The researches have already obtained permission to link the radiology data with the Dutch cancer registry without individual consent. Ethics approval is not required since no additional procedures are performed on patients. However, the study protocol will be submitted soon to the Netherlands Cancer Institute for a feasibility check and subsequently to ethics committees of all participating hospitals. Patients or their parents/legal guardians who have ever objected to the use of their medical data for research purposes in the hospital where CT scan was done will be excluded from the cohort. Personal information of participating subjects will be separated from the analytical data set after completion of data collection and will be kept in a secure place.

Spain
Ethics approvals are underway. Approvals have been received from the first 8 hospitals and data abstraction is underway, without the need for informed consent in these 8 medical centres. In another hospital contacted, the Ethics Committee gave approval for the study as long as prospective patients signed a study specific informed consent form (they did not accept any other solution such as a poster in the waiting room or an additional item on the existing informed consent the parents sign before the procedure). The Committee also gave permission to abstract data retrospectively with no informed consent. Difficulties were then encountered in the first meeting with the head of IT of the hospital. Despite the approval from the ethics committee, he argues that collection of data on retrospective patients violates the patient data protection laws and national coordinators had to go back to the Ethics Committee. One proposal made was to send an information letter to all past patients informing them about the study and asking them to inform the national coordinator if they did not wish to be included, but this has been turned down by the legal services of the hospital and would be logistically and ethically difficult to do. Prospective data collection is about to start in this hospital but a solution to unblock the situation for retrospective patients is actively sought for, including contacts with the Department of Public Health.

Sweden
Ethics approval has been granted for the study. The study will be performed without informed consent. All data will be collected retrospectively.

United Kingdom
In the UK, ethical approval for a study is obtained from one committee, which covers the study for the whole country. The UK study has also been approved by the National Information Governance Board (NIGB) which effectively provides overall consent for all patients without having to obtain individual-level patient consent. To obtain the latter approval, investigators must demonstrate that it is not feasible to get consent, or not ethical to contact subjects to get consent, and that the study is in the public interest.

The approval from NIGB covers only England and Wales, as these are the only countries within the UK that share the same laws. For Scotland and Northern Ireland, separate agreements have been sought using the same arguments as based on the laws in England and Wales.

These approvals allow a retrospective study to access the data under strict data security requirements. The only condition that has been laid down is that identifiable data must be destroyed when they are no longer needed (the authorities are aware that this is a long-term follow-up study, so the investigators are allowed to keep the identifying information under strict data security for as long needed for linkage purposes.

To avoid the need for informed consent, it is not planned to accrue patients prospectively in the United Kingdom.

Norway
Ethical approval was obtained in April 2011. The study will be performed without individual informed consent. All data will be collected retrospectively.
In the application to the ethical committee, it was argued that there are practical, scientific and ethical reasons for not asking for consent: Practically, it would be very difficult, time consuming and expensive to obtain informed consent from everybody who, since1990/1995, at age 0-20 years had a CT-scan taken. It would also be difficult to administer consent forms at the time of CT-scanning, if collection of data was to be done prospectively/concurrently with scans being taken.

Scientifically, non-consent would minimize the study size and compromise power, and most problematic, might bias results due to selective participation. Ethically, and most importantly perhaps for the committees, is that they believe it to be unethical to propose to parents who have let their children undergo CT-scans that it might be dangerous for their child, and even more unethical to suggest to parent/young adults who are about to having a possibly very important scan that this entails a possible cancer risk. Of importance also is that the study itself implies no intervention or risk for the individual subjects.

Data collection at a country level

1. Description

Data collection from PACS and RIS or other type of records will give rise to similar information on included patients and information for prospective follow-up, though the level of detail available for dose reconstruction and assessment of confounders will vary. When possible it is encouraged to perform a thorough inclusion of all potential participants from PACS to reach the expected cohort size and complement it with other type of records such as RIS or paper medical records, which are less accurate in terms of dose reconstruction.

Table 4. Type of records available per country in the radiology departments

Country/cohort	Type of records	Possibility to obtain height and weight		From where?	
		retrospectively	prospectively	retrospectively	prospectively
Belgium	PACS	Not likely	Not possible	PACS	
Denmark	PACS	Not likely	Not likely		
France	RIS/PACS	Not possible	Not possible		
Germany	RIS/PACS	Not likely	Not likely	-	-
Netherlands	RIS/PACS	Not likely	Not likely		
Spain	RIS-PACS	Not likely	Not likely	-	-
Sweden	RIS/PACS	Not likely	Not likely		
UK	Mainly RIS, plus a little paper. PACS is less likely	Not possible	Not possible	-	-
Norway	RIS/ PACS	Not likely	Not likely	-	-

2. Particularities

Belgium
Data can be taken from electronic recording in DICOM format and are available since 2000-2006 (depending on hospital unit and conveniently linking RIS and PACS data). RIS files are available for a long time span of data earlier than that. Specific fields for the weight and height are available in the DICOM but it is not likely that these data will be filled in. However, the diameter and volume of the scanned body section will be collected for each image in thescan. Belgium does not plan to use the PerMoS software.

Denmark
Data can be taken from electronic recording in DICOM format. It is, however, not certain that information about height and weight is documented in these electronic records.

France
RIS information will be the only source of data before 2006. Technical parameters from protocols are available for the majority of children included in the IRSN cohort. Individual films can be retrieved from medical files but dosimetric data are not always available on the film. Electronic files of paediatric patients include hospital department, patient's name, date of birth, hospital ID number, date of the exam, explored anatomical region (head, abdomen, pelvis, etc…), model of CT scanner used.
PACS data are available since 2005-2007, depending on the hospitals. Technical parameters stored in the DICOM header for each procedure (kv, mA, pitch factor, etc.) are not all available, depending on the hospitals. Protocols from radiology department could be used to complete the missing information.

Germany
Manual data extraction from paper records is not feasible.

The electronic patient records (RIS) are the primary source of cohort recruitment and all study relevant information will be abstracted by radiological personnel. Furthermore, it stores the type of performed examination which allows determining the exposed body part. The indication and the result of the examination allow identifying cancer patients and possible confounding by indication. Therefore the RIS is the most relevant database for this study. The introduction of RIS started around 1990 plus minus 8 years. PACS database was introduced around the 2000 year.

On site study personnel will extract RIS data and then process the raw-data and assign a unique pseudonym (study ID (STID)) to each unique patient. The derived data is called base-data. The examinations will be separated from any personal identifier except the STID. These data are called examination-data. From the base-data the cohort (cohort-data) will be derived as shortened birth age, sex, postal code and STID. From raw-data a list of all radiological patient IDs (PATID) with their corresponding STID will be derived, called PACS-list. The data obtained from PACS will be stripped from any personal identifiers whereby the PATID will be replaced by a hash-code. The pseudonymised data is called dose-data and will be transferred to the study server. PerMoS will create locally a linkage table containing PATID and the respective hash-code, called PerMoS-linkage-list. From the PerMoS-linkage-list and the PACS-list the study personal will derive the cohort-dose-linkage-data containing hash-code and STID.
The plain-text personal identifiers from the raw-data will be pseudonymised by specialised software plus the STID, resulting in the radiologic-linkage-data.
From the hospital only the pseudonymised data (examination-data, cohort-data, dose-data, cohort-dose-linkage-data, radiologic-linkage-data) will be taken. All data containing personal identifiers will be left at the hospital.

Netherlands
All relevant electronic radiology records will be retrieved from participating radiology departments. Based on the pilot study and discussions with radiologists from the Radiology Society of the Netherlands, it is expected that this task can be performed, in most cases, by department staff. The researches will offer assistance (by using PerMoS or Conquest software), if needed.
Electronic listings of CT scans are available since approximately 1995, depending on the hospital, with personal information, date and type of scan indication and radiologists report, and the requesting department (RIS). The information collected from PACS includes the images and the DICOM header with technical information on the machine settings during the scan. The PACS is available since approximately 2000.

Spain
The implementation of PACS is heterogeneous across hospital departments and among Autonomous communities, with the most recent being in 2006 at the very large Vall d'Hebron hospital in Barcelona. Most of the hospitals have had RIS or a similar system prior to PACs, but not all of them have reliable information. Information from paper records can be abstracted going back at least 10 years (most 15-20 years) in order to reconstruct the cohort prospectively but most hospitals find it unpractical. Dosimetric data from private hospitals may result difficult to obtain. Fortunately, paediatric population has fewer users of private hospitals. Most hospitals have provided the national coordinator with their own hardware (a virtual machine in one case, an independent server in another) to run the PerMoS software, since they understand this is a long-term follow up study and they don't want to adjust the software setting every time the CREAL personal computer is brought for data extraction.

Sweden
In most of the hospitals, RIS data can be collected from the 1990s. PACS was introduced around 2000, depending on radiology department. Some hospitals have older RIS with data from 1984. The data will be collected from hospitals for all CTs performed on patients born after certain year. The filter will be applied afterwards to retain only patients that were scanned at least once before age 18. Height and weight are rarely stored in RIS.

United Kingdom
The initial RIS request is defined as patients born after a certain year, not under a certain age. Then, this is filtered to ensure that later scans on patients first scanned when they were under 21 years old are also included. At UK RIS, all patient identifiers, dates and types of CT scan are available. Height and weight are not possible to obtain through RIS and number of scans and use of contrast are recorded inconsistently. Indication for the scan is only available for a small percentage of scans.

Norway
The cohort will be established based on the collection of RIS data on all CT scans performed in subjects below 20 years of age from all participating hospital. The object is to include all hospitals in the country. Start of enrolment will depend on when RIS was introduced in the different hospitals, possibly varying between 1995 and 2000. Personal identifiers from the RIS data will be used to extract data from PACS giving the technical parameters form the DICOM header. PACS data are expected to be available from approximately 2003, but this will vary by hospital. Information on most variables is expected to be available, however, data on height and weight is supposed to be missing in most systems. Sources for alternative information on height and weight have so far not been identified.

4. FOLLOW UP

A. PRINCIPLES

The method of data linkage to obtain outcome data will vary between countries (see the country-specific procedures section), but will be designed to ensure that ascertainment of outcomes in the study populations are as high as possible. In most cases, this will involve the use of patient identifiable data.

1. Mortality follow up

1.1 Vital status ascertainment

All persons in the participating cohorts (except for Germany, which will use a life-table approach and France where vital status can be obtained for 50% of the cohort members) will be followed up for mortality in order to establish whether they are dead or alive at the end of the study period. Follow up should be uniform and non-selective for the entire cohort under study. Vital status is ascertained through linkage with national or regional death registries, where possible. In countries where this is not possible, it may involve contacts with local authorities in the commune of residence. Information from other medical records can be used as a supplementary source, but not as the primary source of data for vital status ascertainment. Details of the procedures are described below for each country, as appropriate. In all countries except Germany, both cancer and non-cancer mortality will be analysed. See specific-country procedure section for further details.

Date of last known vital status for individual participants is determined as the earliest of the following three dates: date of end of study, date of death or date of emigration (where available systematically). In all countries where passive mortality follow up is performed, all cohort members whose deaths have not been identified will be assumed to be alive at the end of study date.

1.2 Cause of death ascertainment

For those participants who have died, cause of death information is obtained from vital statistics registries. For external comparisons with country specific rates, coding rules should correspond to those used within each country. For the international study it is important to standardize the assignment of cause of death across countries. Therefore, the minimum information to be obtained for each death is the underlying cause, coded according to ICD-10.

When the underlying cause of death has not yet been assigned according to ICD rules, it should be done. Assignment of cause of death should be performed without knowledge of radiation dose.

2. Morbidity follow up

2.1 Cancer incidence:

For cancer incidence, linkage will be made with national and regional cancer registries as appropriate. Cancer diagnoses will be coded following the International Classification of Diseases for Oncology, 3rd Edition (ICD-O-3), and ICCC3 for children. Codes may change or may have change over the time. This information needs to be recorded.

The following information will be collected for each primary cancer diagnosed in a study subject:

Table 5. Information collected for each primary cancer diagnosed in a study subject

	Description of variable regarding cancer incidence
1	Date of diagnosis
2	ICD-O-3 or ICCC3 code (including 4th digit) and revision number
3	Morphology code and name of morphology classification
4	Best evidence of diagnosis (where possible)
5	Flag indicating information from death certificate only

2.2 Cardiovascular and cerebrovascular disease incidence:

Follow up for incidence of these diseases will be possible through hospital discharge registries (MBDS; Minimum Basic Data Set), medication reimbursement databases and other disease-specific registers depending on the country. See country specific procedures for further details.

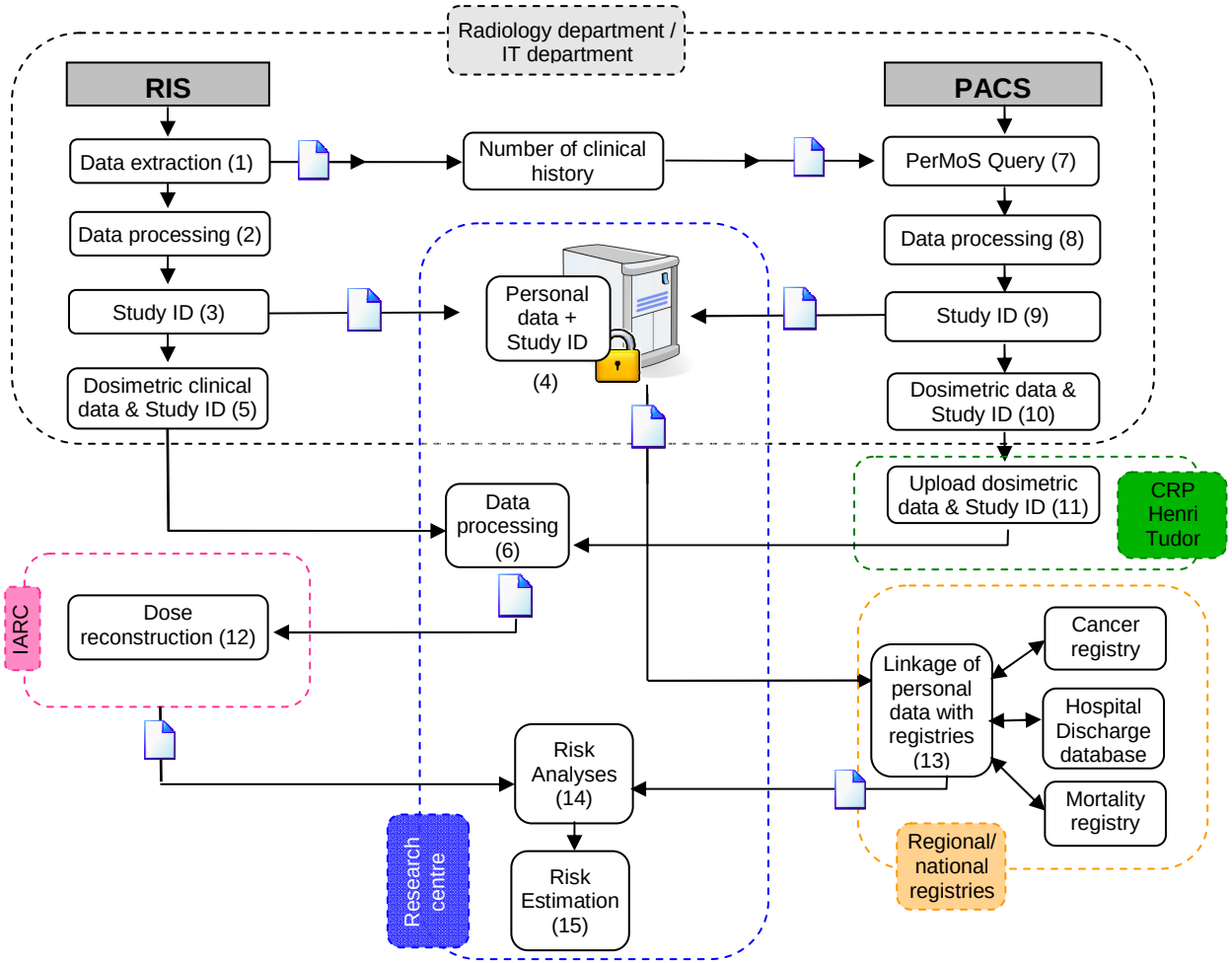
2.3 Other non-cancer outcomes incidence:

Other outcomes of interest in radiation protection today are digestive and respiratory diseases (similar risk estimates have been seen among a-bomb survivors than those for cardiovascular and cerebrovascular diseases). See country specific procedures for further details. The possibility of linking to the European Bone Marrow Transplant Registry should also be considered in some countries.

3. Emigration follow-up

Emigration will not be identified completely in most countries. The information available in a few countries will inform the study about the magnitude of the possible problem. The potential impact in terms of missed outcomes of interest and of overestimated person years at risk will be assessed.

4. Data flow summary



1. When RIS available, extraction of the specific variables from the radiologic records stored in the RIS (Radiology Information System) for those patients following the inclusion criteria
2. These data is processed and adjusted.
3. Identifiable personal data (normally name, surname and birth date, but depending on the variables available on each registry) is extracted from the database and a Study ID is assigned to each patient. In Germany they will assign a hash-code using Munich University software. The rest of the countries may use the Study id structure suggested at the beginning of section 2.
4. A file containing the Study ID and the identifiable personal data will be created and stored at the research centre or at the hospital, depending on the requirements of each specific hospital. Strict security measures will be applied to assure data protection.
5. An excel file (or any convenient type of file) will be released from the hospital containing the desired variables for dose reconstruction and some other clinical variables of interest.
6. Data adjustment and processing, if needed.
7. PerMoS software will query the CT scans of patients following the inclusion criteria by their number of clinical history (obtained through RIS).
8. The software will eliminate the images and keep only the DICOM header containing the CT technical parameters.
9. Identifiable personal data (name, surname and birth date) is extracted from the database and a Study ID is assigned to each patient.
10. Only dosimetric data and the study ID is kept for analyses. This may be kept at the hospital, at the research centre or directly upload to the Luxembourg server.
11. Optional step of uploading non identifiable information.
12. Physic and Technical parameters of CT scan will be sent to IARC for organ-dose reconstruction.
13. Personal data will be useful for linkage to the registries of interest, normally cancer and mortality registries and other databases.
14. Risk analyses will be performed in order to study the association between CT scan type, frequency and cumulative doses of ionizing radiation and risk of developing leukaemia and solid tumours.
15. Risk estimates will be provided.

B. COUNTRY SPECIFIC PROCEDURES

1. Summary table

Table 6. Specific sources of follow up for mortality, morbidity and emigration per country

Country/cohort	Mortality follow up	Morbidity follow up			Emigration follow up
		Cancer incidence	Cardiovascular and cerebrovascular incidence	Other non-cancer outcomes	
Belgium	From the National Cancer Registry; total mortality can be obtained for the entire cohort	National Cancer Registry	Not likely (information from health insurance records is theoretically available but difficult to obtain due to the privacy protection issues)	No	No
Denmark	Central population registry	National Cancer Registry	National Hospital discharge registry	National Hospital discharge registry	Central population registry
France	For about 30% of the study population	Childhood Cancer Registry	National Health insurance database of reimbursement of medication and SNIIRAM (Système National d'Informations Inter Régions d'Assurance Maladie)	Health insurance records	No
Germany	Life-table approach	Childhood cancer registry	No	No	No
Netherlands	Central Bureau of Genealogy (CBG)	Netherlands Cancer Registry	Hospital discharge registries (not sure if feasible)	Hospital discharge registries (not sure if feasible)	No
Spain	Autonomous Community Mortality registry	Cancer registries of the different autonomous communities and national childhood cancer	Centralised hospital discharge database (CMBD)	Health insurance records	No
Sweden	National Causes of Death Registry	National Cancer Registry	Hospital discharge registries and medication reimbursement databases	Hospital discharge registries	Yes
UK	NHSCR	National registry	No	No	NHSCR
Norway	National Causes of Death Registry	Cancer Registry of Norway	Hospital discharge registries and medication reimbursement databases	Hospital discharge registries	Yes

2. Particularities

Belgium

A National Cancer Registry exists with good coverage in Belgium. A linkage with the cohort is feasible through the National Registration Number. For the entire country, the coverage is almost complete since 2004. Before then, the registry had a reasonable coverage since 1999 in Flanders and is almost complete from 2002 in the Flemish part of the country. As the currently participating countries are in Flanders, linkage for these hospitals will therefore be possible since 2002. Before 2002, the coverage is less complete.

Denmark

Automated follow up via the National Cancer Registry is possible for cancer at all ages and follow-up at the National Hospital Discharge Registry for hospitalisations of other chronic diseases.

France

In France, vital status will be obtained for a part of the population but not for the whole because of the lack of birth place for some of the children. This information is stored in a hospital database but there is no automatic linkage with IRSN data. This information will be extracted as often as possible, even though it depends on the IT department and on the linkage way (through patient ID and not the name of the patient). The complexity and amount of work needed to recover this information (contact with other people in the centre, delay to obtain this information, lack of information for the oldest patients) forecast that only 50% of the vital status will be recovered. Fortunately, the death rate in childhood is expected to be low even in this ill population. Efforts to increase this percentage will be done through linkage with other hospital database.

As the population-based Childhood Cancer Registry in France has been in operation since 2000, the inclusion of children is limited to those who were born after 1994 in order to be able to check manually the possible occurrence of cancer before 2000 in the study population. Until now, the registry follow-up was limited to 15 years of age, so it was decided not to include children older than 10 years because of the lack of follow-up, even with the future possibility of extending the cancer registry to young adults of maximum 20 years old. Concerning non-cancer diseases, the use of information from Health Insurance medication reimbursement database is not yet possible and should be considered with caution taking into account difficulties in obtaining ethical agreements. For the analyses in 2015, only cancer incidence will be analysed.

Germany

Morbidity follow-up for non-cancer outcomes and emigration follow up is not planned.
Via record linkage, the pseudonym databases of the radiology department and Germany Childhood Cancer Registry (GCCR) will be checked for matching from paediatric population from 1980 to present. A mortality follow up is possible in Germany; however it's unlikely to be done because childhood mortality rates are very low. Secondly a mortality follow up must be done via local registration offices – a costly and inconvenient procedure. The contributed person years will be calculated from the end of a specific lag period after first examination until whichever of the following comes first: date of first cancer diagnosis, their 15^{th} birthday or the end of the study period. This method of computing person years overestimates the true figure slightly. To compensate for this, (a) patients with high a priori risk will be tagged and (b) person years accumulated after the individual examination have been discounted for non-cancer mortality by multiplying person-years by the appropriate survival rates. This method was already applied in previous studies.

The Netherlands
Cancer incidence information will be obtained by record linkage with the Netherlands Cancer Registry. In addition to the Cancer registry, for cancer incidence follow-up the researches will use PALGA, the Dutch network and national database of histology and cytopathology. Linkage with PALGA will follow the same procedure as with the Cancer registry. The essential advantage of PALGA is that case ascertainment is complete until two weeks prior to the linkage. Vital status and date of death data from the Central Bureau of Genealogy (SBG), which receive death certificate information for each decedent listed in municipal registries, will be used to exclude deceased persons from the cohort accumulation of person-time.

Spain
Population-based cancer registries are regional and not homogeneous over the country, and this has been a critical criterion when choosing the participating regions for the Spanish cohort. National Institute of Statistics provides data on life status but does not provide cause of death, so its data will be used for double check the status of participants. Regional mortality registries in the participating areas will link the patients with their status and provide us with cause of death, in case it has occurred. Cancer registry is just starting in Catalunya region (even though Girona and Tarragona had registries since 1995 and 1980 respectively). Valencia has a childhood cancer registry running on since 2000 and Basque country since 1986. Andalucía has a similar situation as Catalunya with a small region registry operating since 1985 and a regional registry just starting. Other non-cancer outcomes (including cardiovascular and cerebrovascular diseases) will be obtained from the Hospital Discharge file, which is managed at an autonomous community level. Follow up on emigration is not feasible.

Sweden
Cancer incidence follow-up is feasible through linkage with the National Cancer Registry using the national PID. A possible challenge is the identification of patients who had CT procedures in the first 2 weeks of life before they get national PID.

United Kingdom
Exposed individuals are being flagged at the National Health Service Central Registries from where cancer incidence through 2009 will be ascertained in the first instance. The estimated follow-up will cover approximately 2.3 million person years, with an expected number of incident leukaemia and brain cancer cases of 58 and 43 respectively, in the absence of exposure. The inclusion of additional records for later scans would be feasible in the UK using the existing protocol.

Norway
In Norway, information on vital status and emigration status will be done by linkage to the National Causes of Death Registry by the use of the unique personal identification number given to all Norwegians at birth. Information on cancer diagnoses will come from linkage to the Cancer Registry of Norway using the same identifier. Linkage to the Medical Birth Registry will give individual information on the presence of Down's syndrome and birth defects. Linkage to hospital discharge registries and pharmaceutical registries is possible for a restricted part of the follow-up period, but has not yet been applied for or planned.

5. POSSIBLE CONFOUNDING VARIABLES

A. PRINCIPLES

No direct information is available systematically in most of the cohorts on factors such as education, socioeconomic status, diet, other life style factors associated with cancer risk, and ionizing radiation exposures other than those coming from CT scans that may be related both to radiation dose and to cancer risk.

1. Socio-economic status

Socio-economic characteristics are known to be associated with a number of health outcomes, including cancer incidence and mortality. Certain socio-economic strata of children may entail a higher availability to diagnostic techniques that have an elevated cost, and therefore that could mean a different level of received dose, a confounding effect would result. When possible, measures of socio economic status (SES) will be developed to take account of the possible confounding effects of life style factors. The SES could be based on parents' job title or education level if available, or on geographical area estimates based on postal code of the patients address at the time of the first CT scan.

The SES classification will inevitably be country specific (see country specific procedures section). Three to five categories per SES variable should be adequate.

2. Confounding by indication

CT scans related to the diagnosis of an eligible cancer or performed for symptoms caused by an underlying non diagnosed cancer should be excluded from the calculation of exposure. In the analyses phase this will be taken into account and only CT scans that had been undertaken a minimum amount of time (e.g. 2 years for leukaemia and 5 years for brain tumours) prior to diagnosis date (cases) will be included in the analyses, so scanning date is crucial for this purpose. Longer lag intervals carry the risk of excluding relevant CT scans from exposure calculations and therefore leading to attenuated estimated risks. Also variable lag intervals will be used to select an appropriate interval on the basis of goodness of model fit.

The indications for a CT will be analysed and based on that then categorised into risk groups by UMC and IRSN. Risk groups will be developed during the German feasibility study. Also, indications for CTs will be reviewed by a small group of physicians and radiologists and subjects flagged if there is a possibility of confounding by indication, always depending on the source of information. Since indication for scan will be a free text, a system to mine this information should be developed. For instance, by stratifying by modality, one might identify classes or types of indications and search for specific words to categorise the information.

NOTE: The German feasibility study uses the information available in RIS, namely indication, results and clinical information. For data processing and risk group ascertainment, specialised software will be used. The feasibility of this process will be evaluated and recommendation will be made.

To assess the magnitude of the confounding by indication effect, stratified analyses will be performed as part of WP 6. UNEW will provide countries with an idea of the impact of this confounding by indication on the study results.

Each country/cohort has to establish the way to identify cancer patients. See country-specific section for further details.

3. Confounding by other risk factors of cancer

Groups of higher cancer incidence risk will be defined based on the groups defined in the RICC study (previous study on conventional x-rays in children performed by UMC (Hammer RadRes 2009). They should include factors such as Down syndrome, Klinefelter syndrome, mesangeal sclerosis leading to early renal failure, hereditary retinoblastoma (Rb), Li-Fraumeni syndrome (LFS), nevoid basal cell carcinoma syndrome (NBCCS), Neurofibromatosis type 1 (NF1) and other genetic disorders that are considered cancer predisposing syndromes. These groups will be defined by bundles of ICD-10 codes at the moment of diagnosis. Patients will be assigned to these groups based on their examination clinical information, indication and result, when available. If the named factors are found, the patients shall be flagged.

IRSN and UMC will exchange their risk group definitions and will collaborate closely in this task.

B. COUNTRY SPECIFIC PROCEDURES

1. Summary tables

Table 7. Specific variables and sources of information to assess SES confounding effect.

Country/cohort	Type of SES variable (social class, parent's education…)	Information recorded	Source of information
Belgium	Geographic estimate	Postal code of home address at time of first CT	RIS
Denmark	Based on parents' education		Statistics Denmark
France	Geographic estimate	Postal code of their home address	RIS
Germany	Geographic estimate	Latest postal code of their home address	RIS
Netherlands	Geographic estimate	Postal code of their home address	Statistics Netherlands
Spain	Geographic estimate	Postal code of their home address	Medical identifying records
Sweden	Based on parents' education	Education registry	Registry kept by Statistics Sweden
UK	Geographic	Home post code	RIS
Norway	Based on parents' education	National education registry	Statistics Norway

Table 8. Specific variables and sources of information to assess confounding for indication effect

Country/cohort	Variables for identification of cancer cases and other high risk factors for cancer	Information recorded	Source of information
Belgium	Cancer diagnoses (1); descriptive statistics for a subsample (2)	Cancer diagnoses (1); indication and results (findings/diagnoses) of the scans (2)	National Cancer Registry (1), sub-study of 200 consecutive children with CT (2)
Denmark	Cancer diagnoses, other relevant diagnoses identified in National registries	ICD-O/ICD -10 diagnoses	National Cancer Registry, National Hospital Discharge Registry
France	Medical diagnoses associated with hospitalisation, cancer diagnoses	Cancer/non cancer	Medical identifying records/Paediatric Cancer Registry
Germany	Indication, results and clinical information	Risk group	RIS
Netherlands	Cancer diagnoses, birth defects (e.g. Down syndrome), CT indication, leukaemogenic drugs	Diagnoses, ICD format, free text	Netherlands Cancer Registry, PALGA, Perinatal Registry, European Bone Marrow Transplant Registry
Spain	Cancer diagnoses	Diagnoses, ICD format	Medical identifying records
Sweden	Cancer diagnoses	Diagnoses, ICD format	Cancer Registry of Sweden, National Inhospital registry
UK	Cancer diagnoses	Diagnoses, ICD format	Medical identifying records
Norway	Cancer diagnoses, Down syndrome	Diagnoses, ICD-format	Cancer Registry of Norway, Medical Birth Registry

2. Particularities

Belgium

Cancer diagnosis prior to the CT scan will be assessed by linkage with the database of the National Cancer Registry and the date of the first CT scan for each patient.
Besides, a study on the indication of CT scans (prescription) and the subsequent results of the CT findings/diagnoses is currently ongoing. A sample of 200 consecutive children will be studied in the participating University Hospital. Descriptive data will be obtained on indication and on eventual other high dose procedures received by these patients in the same hospital.

Denmark

SES can be assessed by individual education level of parents. The education level can most likely be identified for all participating families in the data from Statistics Denmark. Cancer diagnosis and other high risk factors for cancer can be identified in the National Cancer Registry as well as the National Hospital Discharge Registry. The ICD-0 are registered since 1978.

France

In France, SES will be assessed using the postal code of their home address, but information on the postal code is missing for a third of the participants. Medical diagnoses associated with hospitalisation will be available for about 505 of the cohort. No clinical information will be available for patients undergoing CT without hospitalisation. The diagnosis of cancer from 2000 to 2015 will be obtained by linkage with the National paediatric cancer registry.

Germany
It is questionable if spatial SES measures are available for the entire study period. Risk group ascertainment will be only performed if feasibility can be demonstrated.

The Netherlands
SES may be linked with access to healthcare (CT scans) and incidence of childhood cancer. The researches obtained socioeconomic data on ethnicity, price of houses, income, etc. by 6 digit postcode (17 households including 40 people, on average) from Statistics Netherlands. A combined score for adjustment will be constructed by principal component analysis. Confounding by indication due to non-leukaemia diseases could also occur. Candidates are Down syndrome, other congenital disorders or familial cancer syndromes, and other diseases treated with allogeneic bone marrow transplantation, which include conditioning regimens with established leukaemogenic agents. Subjects with those diseases may have more CT scans and do have an elevated risk of leukaemia. The researches will be able to identify those subjects from several sources, including the radiologist report for each CT scan 9as determined in the pilot study), nationwide record linkage with the Perinatal Registry of the Netherlands, in which congenital and other inborn disorders are registered, as well as with the European Bone Marrow Transplant (EBMT) Registry or the registry of malignant and non-malignant conditions at the Dutch Childhood Oncology Group.

Spain
In the Spanish cohort, seems feasible to assign subjects SES based on the postal code home addresses. Previous epidemiological studies carried at CREAL have estimates on SES bases on the postal code.

Sweden
Presence of cancer diagnoses prior to or after CT scan can be verified by the data from the National Cancer Registry with the use of personal identification number.

United Kingdom
In the UK postal code is used to develop a proxy SES. According to the experience in the completed study, extra time may be needed for this task since it took longer than initially thought as postal/ZIP codes are not recorded very well by hospitals.

Norway
The presence of a possible cancer diagnosis prior to, or immediately after, the scan, will be verified by linkage to the cancer registry by the use of the personal identification number.

6. QUALITY ASSURANCE/VALIDATION

A. PRINCIPLES

Different levels of validation are envisaged. Information on specific checks carried out in completed studies would be useful in determining the details of the checks to be used.

1. Descriptive information

Information will be obtained on the procedures and success of project implementation in the different countries. This includes:

- The coverage of the cohort in the participating country and how it was evaluated: This task will be carried out by CREAL, who will develop validation tools that will be provided to all partners to check the quality of the data collected at regular intervals, thus ensuring that any problem can be resolved in a timely fashion. After the first 6 months of data collection and then every year sample data sets will be requested and reviewed by CREAL to identify and remedy any problem in data collection and to ensure compliance with protocol schedules and comparability of data collected.
- The identifiers used for linkage, the percentage of records in which these identifiers were available and the method of linkage used (probabilistic vs. deterministic): all this information will be obtained for each country and centrally reviewed.
- The completeness of the follow-up and how this was validated: Each participating country/cohort will assess its completion and report it in order to assess the differences in vital status, morbidity follow-up and cause of death ascertainment.
- Every participating country will check on the computerization of the data (double entry, etc.) and will perform the agreed (to be determined) quality control on the database.

2. Missing exposure data

The approach chosen for the study in most countries is likely to miss part of the radiological exposure of the study subjects, due to CTs received in childhood in non-participating hospitals, other diagnostic procedures in childhood and procedures received after age 20.

Using the experience of one UK region, where all of the radiological departments are included in the study and information about all scans in subjects born after a certain year is most likely recorded. In UK, the UK data will provide information about the extent of missing information in other countries. At the time of the kick-off meeting it was estimated that about 2% of the patients in that region have had at least one CT scan in a different hospital.

In other countries (see specific country procedures section), some validation of completeness of coverage of CT data would be desirable where feasible. This could be done in the future in the framework of the nested case-control study, with information sought from all hospitals in the region of the hospital in which the first scan has taken place, for all cases and controls. Where this is not feasible, information could be sought for a small sample of the cohort.

Impact of other radiological procedures will be verified in countries/hospitals where information is available or through validation studies.

Missing doses of CT scans due to series of non-recorded images (because of poor image quality) should also be evaluated. It is important to ask if the hospital records every examination that is taken in the patient even if it's not informative due to a poor result. In some countries, it may be possible to evaluate for a sample of patients the total number of CT procedures performed (or other procedures: X-ray, nuclear medicine examinations, etc…)

3. Other checks (suggested)

This will cover both outcome and dose data checks that should be carried out – if applicable - before the data are sent to the National Coordinator Centre:

- Checks of the temporal sequence of dates:
    - date of birth <= date of last known vital status <= date of end of study
- Age at start of study must be in age range of the study population for the particular country
- Vital status and ICD code (e.g., alive subjects with non-blank ICD)
- Consistency between sex and ICD code (e.g., males with cancer of female breast, uterus, cervix, ovary; or females with testis cancer)
- Comparisons of mortality with national rates (via SMR's tabulated by attained age, calendar year, etc.).

B. COUNTRY SPECIFIC PROCEDURES

1. Summary table

Table 9. Validation of coverage completeness of CT data

Country/cohort	Possibility of validation of completeness
Belgium	Missing exposure data: statistics for a subsample of the Belgian population
Denmark	-
France	NO
Germany	Completeness of CT data per patient across different hospitals by cross check between included hospitals and assessment of external vs. in the PACS of the specific hospital is planned No possibility to validate completeness of the CT procedures recorded
Netherlands	Check of paper records of subsets of children born before electronic archiving of CT scans Survey of German and/or Belgian radiology practices near the Dutch border
Spain	NO
Sweden	-
UK	-
Norway	-

Belgium

A subsample of the Belgian population is available regarding the occurrence of medical examinations. These statistics, available from the Health insurance companies, are likely to give an estimation of the contribution of the other radiological procedures to patient exposure. A permission to receive data from this database will be sought in order to investigate the other medical radiation exposures to children who received at least one CT scan, for the available period.

Denmark

It is yet to be decided how to approach this issue in Denmark.

7. UNFORESEEN SITUATIONS

A. PRINCIPLES

This section will cover difficulties or non-foreseen situations encountered when developing the study protocol. It is open to be filled and updated with the new situations the countries may encounter.

1. **Descriptive information**

–Construction of cohorts

–Data collection

–Follow-up

French cohort will not be able to obtain vital status for 80% of the cohort as initially though would be only about 50% and this could be a critical issue that can affect the risk estimation of the study. Germany will be facing a similar situation. Even if mortality in children is low and life tables adjusting for risk estimates of mortality in the study population could be applied, children that have CT scans may have higher rates of mortality. In particular, there will be a (small) group of very sick children with multiple scans and a high fatality rate. Other studies should be used to provide information on the magnitude of childhood mortality rates in these patients; otherwise the number of person-years at risk is overestimated, which would result in an underestimation of a possible association between exposure and disease.

In the Netherland, radiologists' reports for all scans in a large university hospital have been obtained and will be used to screen for keywords with specific software. (Using a standard search routine, showed that there is information on indication and pre-existing conditions, e.g. Down syndrome, and often previous scans are mentioned.)

–Possible confounding variables

–Quality assurance/validation

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Annex 1

Hospital	Scanner1	Scanner2	Scanner3	Scanner4	Software PACs	Management Software