



**HAL**  
open science

## The HARMONIC project: Study design for the assessment of radiation doses and associated cancer risks following cardiac fluoroscopy in childhood.

Richard Harbron, Isabelle Thierry-Chef, M. S. Pearce, Marie Odile Bernier, Serge Dreuil, Estelle Rage, Maria Grazia Andreassi, Eugenio Picano, Steffen Dreger, Hajo Zeeb, et al.

### ► To cite this version:

Richard Harbron, Isabelle Thierry-Chef, M. S. Pearce, Marie Odile Bernier, Serge Dreuil, et al.. The HARMONIC project: Study design for the assessment of radiation doses and associated cancer risks following cardiac fluoroscopy in childhood.. *Journal of Radiological Protection*, 2020, 40 (4), pp.1074. 10.1088/1361-6498/aba66d . hal-03098801

**HAL Id: hal-03098801**

**<https://hal.science/hal-03098801>**

Submitted on 15 Jan 2021

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



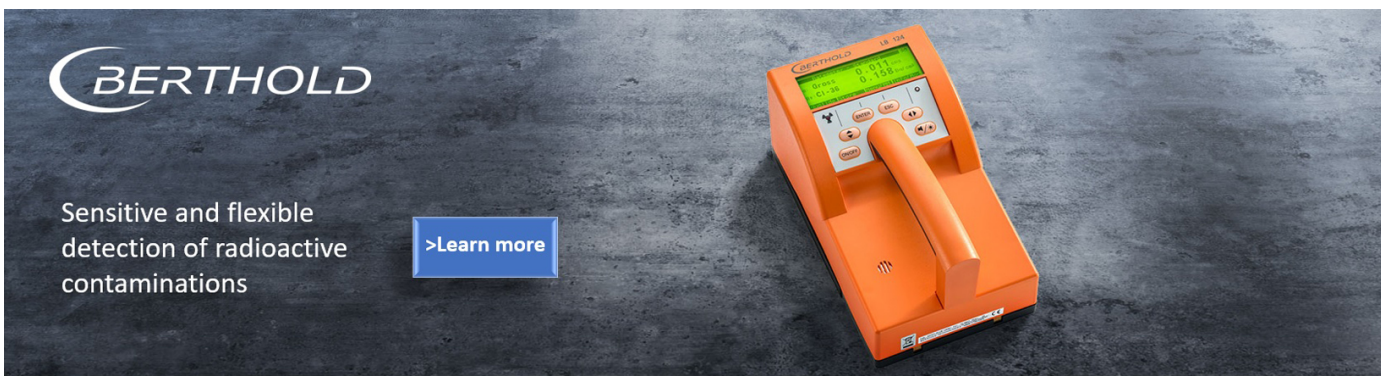
Distributed under a Creative Commons Attribution 4.0 International License

PAPER • OPEN ACCESS

## The HARMONIC project: study design for the assessment of radiation doses and associated cancer risks following cardiac fluoroscopy in childhood

To cite this article: Richard W Harbron *et al* 2020 *J. Radiol. Prot.* **40** 1074

View the [article online](#) for updates and enhancements.



**BERTHOLD**

Sensitive and flexible  
detection of radioactive  
contaminations

>Learn more

# The HARMONIC project: study design for the assessment of radiation doses and associated cancer risks following cardiac fluoroscopy in childhood

Richard W Harbron<sup>1,2,3,4,16</sup> , Isabelle Thierry-Chef<sup>1,2,3</sup> , Mark S Pearce<sup>4</sup> , Marie-Odile Bernier<sup>5</sup> , Serge Dreuil<sup>5</sup> , Estelle Rage<sup>5</sup> , Maria Grazia Andreassi<sup>6</sup> , Eugenio Picano<sup>6</sup> , Steffen Dreger<sup>7</sup> , Hajo Zeeb<sup>7,8</sup> , Hilde Olerud<sup>9</sup> , Utheya Thevathas<sup>9</sup> , Kristina Kjaerheim<sup>10</sup> , Gaute Døhlen<sup>11</sup> , Andreas Jahnen<sup>12</sup> , Johannes Hermen<sup>12</sup> , Vadim Chumak<sup>13</sup> , Elena Bakhanova<sup>13</sup> , Vitalii Voloskyi<sup>13</sup> , David Borrego<sup>14</sup> , Choonsik Lee<sup>14</sup>  and Jérémie Dabin<sup>15</sup> 

<sup>1</sup> Barcelona Institute for Global Health, (ISGlobal), Barcelona, Spain

<sup>2</sup> Universitat Pompeu Fabra (UPF), Barcelona, Spain

<sup>3</sup> CIBER Epidemiología y Salud Pública (CIBERESP), Madrid, Spain

<sup>4</sup> Population Health Sciences Institute, Newcastle University, Newcastle upon Tyne, United Kingdom

<sup>5</sup> Institut de Radioprotection et de Sûreté Nucléaire (IRSN), Fontenay-aux-Roses, France

<sup>6</sup> Istituto di Fisiologia Clinica del CNR, Pisa, Italy

<sup>7</sup> Leibniz Institute for Prevention Research and Epidemiology (BIPS), Bremen, Germany

<sup>8</sup> Health Sciences Bremen, University of Bremen, Bremen, Germany

<sup>9</sup> Faculty of Health and Social Sciences, University of South-Eastern Norway, Kongsberg, Norway

<sup>10</sup> Cancer Registry of Norway—Institute of Population-based Cancer Research, Department of Research, Oslo, Norway

<sup>11</sup> Department of Pediatric Cardiology, Oslo University Hospital, Norway

<sup>12</sup> Luxembourg Institute of Science and Technology (LIST), Esch-sur-Alzette, Luxembourg

<sup>13</sup> National Research Center for Radiation Medicine (NRCRM), Kyiv, Ukraine

<sup>14</sup> Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, 9609 Medical Center Dr, Bethesda, MD 20892-9778, United States of America

<sup>15</sup> Belgian Nuclear Research Centre, SCK CEN, Mol, Belgium

<sup>16</sup> Author to whom any correspondence should be addressed.



Original content from this work may be used under the terms of the [Creative Commons Attribution 4.0 licence](https://creativecommons.org/licenses/by/4.0/). Any further distribution of this work must maintain attribution to the author(s) and the title of the work, journal citation and DOI.

E-mail: [Richard.harbron@ncl.ac.uk](mailto:Richard.harbron@ncl.ac.uk)

Received 3 June 2020; revised 13 July 2020

Accepted for publication 15 July 2020

Published 24 September 2020



CrossMark

### Abstract

The HARMONIC project (Health Effects of Cardiac Fluoroscopy and Modern Radiotherapy in Paediatrics) is a European study aiming to improve our understanding of the long-term health risks from radiation exposures in childhood and early adulthood. Here, we present the study design for the cardiac fluoroscopy component of HARMONIC. A pooled cohort of approximately 100 000 patients who underwent cardiac fluoroscopy procedures in Belgium, France, Germany, Italy, Norway, Spain or the UK, while aged under 22 years, will be established from hospital records and/or insurance claims data. Doses to individual organs will be estimated from dose indicators recorded at the time of examination, using a lookup-table-based dosimetry system produced using Monte Carlo radiation transport simulations and anatomically realistic computational phantom models. Information on beam geometry and x-ray energy spectra will be obtained from a representative sample of radiation dose structured reports. Uncertainties in dose estimates will be modelled using 2D Monte Carlo methods. The cohort will be followed up using national registries and insurance records to determine vital status and cancer incidence. Information on organ transplantation (a major risk factor for cancer development in this patient group) and/or other conditions predisposing to cancer will be obtained from national or local registries and health insurance data, depending on country. The relationship between estimated radiation dose and cancer risk will be investigated using regression modelling. Results will improve information for patients and parents and aid clinicians in managing and implementing changes to reduce radiation risks without compromising medical benefits.

Keywords: cardiac fluoroscopy, cancer risks, epidemiology, Monte Carlo

(Some figures may appear in colour only in the online journal)

## 1. Introduction

Survival rates for congenital heart disease have improved markedly in recent decades [1–3], leading to increased focus on the long-term complications of treatment. Cardiology relies extensively on the use of ionising radiation, in the form of general radiography, computed tomography (CT) and x-ray guided trans-catheter interventions [3–6]. Radiation exposure is associated with a number of adverse effects including an increase in the lifetime risk of developing cancer (e.g. [7]) and, at high doses, impairment of tissue function through the effects of excessive cell killing [8]. These risks may be justified, if outweighed by the diagnostic or therapeutic advantage of the exposure. When risks are uncertain, justification becomes difficult and confusion among clinicians, patients and parents becomes inevitable.

Epidemiology has played an important role in assessing the long-term health effects of radiation exposure [9], and will continue to do so while research investigating specific

biomarkers of radiation induced disease is ongoing. However, substantial uncertainties remain for doses below 100 mGy, non-photon exposures (including protons and neutrons) and for exposures occurring very early in life [10]. The HARMONIC project (Health Effects of Cardiac Fluoroscopy and Modern Radiotherapy in Paediatrics) (<https://harmonicproject.eu/>) is a five-year European Commission funded study aiming to improve understanding of the long-term health risks from ionising radiation exposure in children and young adults, helping to further improve quality of life of these patients. The project addresses exposures not covered by existing or recently completed European paediatric radiation research programs including MEDIRAD (childhood CT and radioiodine and breast radiotherapy in adults) and EPI-CT (childhood CT). The cardiac and radiotherapy components of HARMONIC are bridged by a biological component, which will investigate biomarkers of radiation exposure and predictors of adverse effects.

Here, we describe the cardiac fluoroscopy component of HARMONIC, including the study rationale, cohort establishment, the methods used to estimate organ doses and epidemiological analysis. Along the way, we will highlight a number of challenges faced by the study (and other similar studies) and the proposed methods for addressing them.

### 1.1. Background

The term ‘cardiac fluoroscopy’ encompasses a range of x-ray guided procedures used to diagnose, monitor and treat a variety of heart conditions, including cardiac catheterisations, electrophysiology studies and pacemaker insertions. These procedures play an important role in the management of various forms of congenital and acquired heart disease [3], including anomalous ducts and septal defects, narrowed arteries, veins and valves, electrophysiological disorders and monitoring transplant allografts. In the UK, around 5000 such procedures are performed each year in children <16 years [11].

Cardiac fluoroscopy often involves prolonged exposure to x-rays, however. Reported estimated bone marrow doses frequently exceeded 10 mGy per procedure before 2000 [12], although have fallen to 1 or 2 mGy in recent years [12–15]. Lung and heart doses are typically in the regions of 5–20 mGy, though often exceed 100 mGy [13–16]. Breast dose varies strongly with beam angle and field size, ranging from <1 to over 100 mGy [12]. Cumulative organ doses from multiple procedures may occasionally exceed 1000 mGy [12, 17]

The risks from these doses are unclear. Only a small handful of studies have attempted a direct epidemiological analysis of cancer risks from cardiac fluoroscopy in childhood [18–22]. Two studies of a Canadian cohort ( $n = 4891$ , reduced to 3915 in the second analysis) found no evidence of raised incidence or mortality for cancer [18, 20], while a study of 674 Israeli children reported significantly raised incidence, based on 11 observed cases versus 4.75 expected [21]. A recent study of 11 270 children who received cardiac catheterisations in the UK [22] found an increased incidence of cancer, although this appeared to be largely associated with transplantation, rather than radiation exposure. Another recent study [19] reported 16 incident cases versus 3.64 expected among a cohort of 2770 German children exposed below age one year. All the above studies featured relatively small sample sizes, limiting power to detect excess risks at low doses. Other studies have reported increased cancer incidence among adults with congenital heart disease [23] or individuals with congenital heart disease irrespective of radiation exposure (e.g. [24, 25, 62]).

### 1.2. Rationale for study

Currently, the cancer risks from cardiac fluoroscopy can only be estimated using models based on other exposures (namely cohorts of atomic bombing survivors and nuclear workers)

(e.g. [26]). These risk projections rely on an assumed, though unproven, linear no-threshold (LNT) relationship between dose and excess cancer risk [27]. Multiple simplifying assumptions regarding the impact of age-at-exposure and attained age since exposure are made [26]. Risk estimates are subject to large uncertainties (e.g. as represented by wide confidence intervals) and do not consider individual radiosensitivity. There is a possibility, therefore, that these projected risks significantly under- or overestimate true risks. This lack of information may ultimately limit the quality of patient care.

The cardiac fluoroscopy component of HARMONIC is designed to complement ongoing studies of the cancer risks following CT scans in childhood, including EPI-CT [28] and MEDIRAD ([www.medirad-project.eu/](http://www.medirad-project.eu/)). Although far fewer cardiac fluoroscopy procedures are performed each year, compared to CT scans, the epidemiological analysis of cancer risks following these exposures has certain advantages over CT studies. Firstly, cardiac fluoroscopy is not directly used in the diagnosis, treatment and follow-up of cancer, thus the potential for reverse causality is, in theory, reduced. This is in contrast to CT which is used extensively in cancer diagnosis and management. Secondly, cardiac fluoroscopy is used in the management of very young patients (<5 years) for which current information on the risks from radiation exposure is limited [10]. Thirdly, records of cardiac fluoroscopy usually include dose indicators recorded at the time of examination (typically kerma area product, air kerma at a reference point, and/or total fluoroscopy time), which may be used to inform the exposure assessment to derive procedure specific dose estimates. This is significant given the large inter-procedure dose variation, with in-field organ doses ranging from close to zero (e.g. due to procedure abandonment at an early stage) to several hundred mGy for more complex procedures [12]. Procedure-specific dose indicators also allow us to distinguish between genuine x-ray guided procedures and non-radiological procedures (e.g. sedation) also recorded in examination records. In CT cohorts, these non-radiological procedures were often listed simply as 'unknown' in the radiology information system (RIS), making them difficult to distinguish from actual CT scans, especially as dose indicators such as computed tomography dose index (CTDI) are not usually recorded in the RIS. Furthermore, a single RIS entry for a CT scan may, in reality, represent a multi-phase examination with two or more scans, with or without contrast media enhancement. Such issues are largely avoided with cardiac fluoroscopy, provided procedure specific dose indicators are recorded.

## 2. Study methodology

The HARMONIC study will use a common methodology similar to that used in the EPI-CT study [28], though with a number of modifications.

### 2.1. Cohort establishment

National cohorts have previously been established in France [29] and the UK [22]. HARMONIC will involve further expansion and increased follow-up of these two cohorts, while also establishing new cohorts in Belgium, Italy, Germany, Norway and Spain. These seven national cohorts will then be pooled, giving a combined cohort of up to 100 000 individuals (table 1).

*Inclusion criteria.* (a) Underwent at least one cardiac fluoroscopy procedure (catheterisation of heart and surrounding vessels, including electrophysiology studies, and pacemaker insertion/revision) in participating country.

**Table 1.** Summary of data from participating countries.

Country:	Current cohort size	Expected cohort size	Age range (years)	Earliest available data	Examination information data source	Cancer diagnosis information source	Transplant registry
Belgium	0	6000	0–18	2004	RIS, logbooks	National cancer registry	Yes
France	19 000	19 000	0–16	2000	RIS, HID	National childhood cancer registry (0–18 y)	No
Germany	0	34 000	0–18	2004	HID, RIS, logbooks	National childhood cancer registry (0–18 y) <sup>a</sup>	No
Italy	0	1000	0–18	2017	RIS, logbooks	Clinical follow-up	No
Norway	0	8000	0–18	1990	RIS, DMS	National disease registry	No
Spain	0	5000	0–21	1995	Hospital DMS	Medical hospital discharge records	Yes
United Kingdom	11 270	30 000	0–22	1991	RIS, DMS, logbooks	National disease registry	Yes
<b>Total</b>	<b>30 270</b>	<b>103 000</b>					

RIS = Radiology information system, DMS = Dose management system, HID = Health insurance data.

<sup>a</sup>German Childhood Cancer Registry; there are adult cancer registries in all federal states as well.



(b) Age under 22 years at the time of procedure (<17 years in France due to cancer registry coverage).

(c) Resident of participating country, to facilitate follow-up.

*Exclusion criteria.* (a) Patients diagnosed with a benign or malignant tumour before the first cardiac fluoroscopy procedure.

(b) Patients undergoing Hickman or peripherally inserted central catheter (PICC) insertions or fluoroscopically guided pericardial effusion drainage only, with no other cardiac fluoroscopy procedures (these procedures are used extensively in cancer treatment).

Data will be collected as far back as examination records exist and cancer registry linkage is possible (table 1) and up to 2021. For all countries except Germany, cohorts will primarily be established through a download of the RIS at participating hospitals. In some cases, information may be stored in a dedicated dose management system (DMS). If sufficient patient identifiers are recorded, DMS data may be sufficient alone, without RIS linkage. Older data may be recorded in paper log book form and will be manually transcribed. The German cohort will be established from insurance claims records and hospital records, with dosimetric data sampled from two university medical centres in Germany and used to estimate national figures (methodologies for handling the inevitable uncertainties inherent in this approach are discussed later).

As a minimum, the following data will be obtained: (1) patient identifiers (name, date of birth, hospital number, health service ID number), (2) examination type, (3) date of procedure, and (4) dose indicators (described below). Cohort members will be assigned a pseudo-anonymous ID number and analysis will be performed using these ID numbers, with identifiable data being used only for registry linkage at the local/national level.

## 2.2. Dose estimation

The estimation of absorbed dose to individual organs is an essential component of HARMONIC. Given the large inter-procedure variability in radiation exposures [12], patient- and procedure-specific dose estimates are essential. Kerma area product ( $P_{KA}$ ) is recorded for the majority of procedures recorded in hospital RIS records, and has been so for the last 20 years or more.  $P_{KA}$  is a dose indicator, equal to the collision air kerma, as measured by a large area ionisation chamber attached to the x-ray tube, multiplied by beam area. In some fluoroscopy equipment,  $P_{KA}$  is estimated based on exposure factors. If only fluoroscopic screening time (FT) is recorded for a procedure, we will estimate  $P_{KA}$  based on the relationship between FT and  $P_{KA}$  for the same equipment type and patient size, for procedures for which both figures are recorded. If neither  $P_{KA}$  nor FT are available, doses will be imputed based on procedure-specific average doses for the same time period. This latter approach has been used in studies investigating cancer risks from CT scans (e.g. [30, 31, 63]).

*Challenge 1.* The study requires the rapid estimation of organ doses for a large number of examinations (100 000+). Performing individual physical measurements or Monte Carlo simulations for each procedure would not be practical.

*Proposed solution.* We will use a 'lookup-table' (LUT) approach, in which patient doses are estimated using pre-calculated conversion factors relating dose indicators to different organ doses.



Conceptually, the LUT approach is relatively simple. Doses can be estimated using physical measurements or Monte Carlo simulations for a given set of conditions (e.g. particular beam angle, patient size, x-ray energy spectrum) and the results used to estimate doses for any exposures in which conditions are similar. In its simplest form, the approach may involve a single conversion factor relating  $P_{KA}$  to patient dose for a single combination of conditions. This can be expanded to produce a table of conversion factors for a range of different conditions, e.g. different beam angles. All that remains is to pick the most appropriate conversion factor from the table for a given exposure. Examples of LUT-based dosimetry systems include NCICT [32] and CalDoseX [33]. Dose estimates for the first UK cardiac catheterisation study [22] were obtained using an earlier version of the 'CD16' LUT-based dosimetry system [34]. HARMONIC will involve a similar approach to CD16, updating LUTs using more realistic computational anatomical models.

The LUT approach has the advantage of vastly increased speed, relative to performing individual physical measurements or Monte Carlo simulations for each examination. Doses for thousands of examinations can be estimated in a matter of minutes. The major disadvantage of the LUT approach is that doses can only be estimated for conditions for which appropriate conversion factors have been calculated. Larger LUTs covering a wider range of parameters can be created, but require a longer initial setup time. This limitation will be overcome with the use of high-performance computer servers with  $\approx 10^4$  processors.

For HARMONIC, we will construct LUTs of conversion factors relating organ dose to  $P_{KA}$  ( $\text{mGy}/\text{Gy cm}^2$ ) for 851 beam angles, ranging from  $90^\circ$  right anterior oblique (right lateral) to  $90^\circ$  left anterior oblique (left lateral) and  $55^\circ$  cranial to  $55^\circ$  caudal in  $5^\circ$  intervals), each for male and female versions of six different phantom sizes (new born, 1-, 5-, 10-, 15-years and adult), at least two different field sizes, and for at least ten different x-ray energy spectra. Conversion factors will be calculated using the general purpose Monte Carlo radiation transport code MCNPX v2.7 (Los Alamos Laboratories, NM, USA) [35]. We will use anatomically realistic paediatric and adult voxel phantoms published by the International Commission on Radiological Protection (ICRP) [36]. Doses will be calculated for 58 organs and tissue structures including active bone marrow, breasts, oesophagus, thyroid, heart and associated sub-structures, and lungs. For bilateral organs (the lungs and breasts) separate left and right doses will be reported as there is likely to be significant heterogeneity in the dose distribution. Doses will be estimated based on patient age. We will use linear interpolation to estimate doses for patient ages in between the two closest phantom sizes. Height and weight are often recorded in the RIS and DMS and can, in theory, allow better matching between patients and appropriate phantoms, and allow for potential modelling of the impact of BMI on organ doses. Height and weight may be less reliable, however, as they are often simply obtained by asking the parents.

Doses will be adjusted for beam energy as represented by half value layer (HVL). This simplifies calculations as multiple factors influencing energy spectra, including tube potential, added and inherent filtration and anode angle are combined into a single figure. For the CD16 dosimetry system [34], doses were first estimated for a single 'reference' 1st HVL, then adjusted to the desired energy using a correction factor calculated by fitting a polynomial to the relationship between HVL and dose relative to the reference HVL. A similar approach will be used for HARMONIC. Although convenient, the HVL approach introduces errors as the same HVL may be produced by different combinations of parameters, each of which may yield a different organ dose per unit  $P_{KA}$ . This could be remedied by using both 1st and 2nd HVL in energy corrections.

A graphical user interface (GUI), similar to that used for NCICT [32], will be developed to pick the appropriate conversion factor from the lookup tables for specified conditions. This

GUI will be made freely available for use in research and audit programs. A batch mode will be included, enabling automated calculations for a multiple procedures and patients.

*Challenge 2.* Producing a dosimetry system capable of estimating organ doses for a given set of input conditions is only half the problem. A second major challenge is knowing which of these input conditions to use for a given clinical procedure. Which beam angles, field size or beam energy spectrum should be selected? These parameters typically vary during a single procedure, which may involve tens or even hundreds of individual exposures.

*Proposed solution.* Exposure parameters will be estimated based on procedure type, patient age and equipment type using various sources of information, including a sample of radiation dose structured reports.

Each specific cardiac fluoroscopy procedure type is associated with a particular set of beam angles, designed to best visualise the anatomy under investigation. Many procedures, including aortic and pulmonary valvuloplasty, utilise posterior-anterior (PA) and left lateral projections only. Other procedures, such as coronary angiography, utilise complex combinations of oblique beam angles. The procedure type, therefore, defines the beam angles likely to have been used, though there is still considerable scope for variation.

The main source of information on beam angles will be a sample of radiation dose structured reports (RDSR) [37]. These contain information on the beam angle, tube potential, added filtration and table position for each individual exposure during a procedure. RDSRs are stored as image metadata in the DICOM header format in the hospitals' PACS network. DMSs have been introduced recently and can be used to access RDSR data. Several existing free and/or open source software tools such as OpenREM [38] are available to extract RDSR data. We are planning to develop our own easily installable software, specifically tailored to the needs of the study. Firstly, the software will determine the examinations to include in the study. Secondly, all DICOM metadata (RDSR and alternatively DICOM image headers) needed for the dose reconstruction will be retrieved and collected. The software will only export pseudonymised data records containing the required information for the dose reconstruction. We plan to obtain a sample of RDSRs representing the most common procedure types, from at least one hospital from each participating country. We aim to obtain at least 100 RDSRs for each procedure type at each centre. Ideally, we will obtain RDSRs representing different fluoroscopy equipment manufacturers (Philips, Siemens etc).

HARMONIC will involve dose estimation for procedures performed as far back as the 1990s, i.e. well before the introduction of RDSRs in 2005. It is not clear if the typical beam angles used for cardiac fluoroscopy have changed over time and, consequently, whether RDSRs are an appropriate source of information for pre-RDSR era examinations. Other information on beam angles will also be obtained from questionnaires, logbook records of beam angles, simplified dose reports (for digital acquisitions only) and biplane  $P_{KA}$  records.

The sample of RDSRs will also be used to estimate beam energy spectra for recent examinations. All RDSR-capable fluoroscopy equipment has the ability to automatically vary tube potential (kV) and added filtration, depending on attenuator thickness. If the equipment type, exam type and patient size are known, it is possible to estimate kV and filtration. For examinations performed using pre-RDSR era equipment (for which automatic variation of filtration thickness was not always implemented), beam energy will be estimated from values quoted in previous publications, manufacturer specifications, and quality assurance reports.

Doses reconstructed using estimated beam angles and x-ray energy spectra will be validated through comparison with dose reconstructions using procedure-specific beam angle/energy information obtained from RDSRs.

### 2.3. Other radiological procedures

As part of disease management, cohort members are exposed to other medical radiation sources in addition to cardiac fluoroscopy, including CT scans, nuclear medicine, non-cardiac fluoroscopy and general radiography. Not accounting for these exposures may confound or bias the apparent dose response relationship. The available evidence suggests CT and fluoroscopy represent the dominant medical radiation exposures among children with heart disease, accounting for around 80%–95% of cumulative effective dose [4–6]. Some patients, most notably those with dilated cardiomyopathy and heart failure, may undergo dozens of general radiography procedures, with estimated cumulative effective doses reaching several mSv [5]. It is therefore preferable to gather data on such procedures.

Where possible, information on CT scans can be obtained from the EPI-CT database for all countries except Italy (which did not take part in EPI-CT). This linkage may not be possible for the whole study period. Primary data collection for EPI-CT ended in 2014, though the MEDIRAD project will involve collection of data on additional scans received by a subset of EPI-CT cohort members beyond this date. For countries with information available from health insurance databases, i.e. in France and Germany, information on all radiological procedures can be retrieved. Based on this information and on data collection periods with the most complete information on non-cardiac-fluoroscopy will be used to impute missing dose for periods and countries with incomplete information using 2D Monte Carlo methods (described below). It is anticipated that doses for CT scans will be obtained from the EPI-CT database or directly using NCICT [32]. Doses from nuclear medicine will be estimated using NCINM, a new tool developed by the National Cancer Institute [39].

**Challenge 3.** Uncertainties in dose estimates are potentially large. These uncertainties are due to (1) errors in the Monte Carlo simulations used to calculate conversion factors and (2) lack of knowledge of which conversion factor to use. The former can be minimised by using a well benchmarked code such as MCNP and running a sufficient number of particles to reduce simulation errors to <1%. The latter are more difficult to control. Breast dose, for example, is especially sensitive to small changes in beam angle [12], while dose to all organs vary by a factor of two or more with beam energy. A list of uncertainty sources is given in table 2. Shared uncertainties occur when a variable is fixed for the whole cohort, or for a sub-cohort. For example, uncertainty in inherent filtration is shared between all cohort members exposed using the same equipment. Data will be collected over a long time period, during which the availability of exposure metadata ranges from almost nothing to highly detailed structured reports.

**Proposed solution.** We will assess uncertainties using a 2D Monte Carlo (2DMC) methodology [40, 41]. Rather than produce a single ‘best guess’ dose estimate, the 2DMC approach produces multiple ‘realisations’ of potentially true doses using probability density functions (PDFs) of input parameters, e.g. beam angle, x-ray energy etc. An example is shown in figure 1. The 2DMC method ensures the correct relationship between individual uncertainty sources is maintained while correlation of doses for persons with similar attributes is also maintained.

**Table 2.** Sources of uncertainty in dose estimates.

	Uncertainty source	Can be incorporated in 2DMC?	Shared or unshared
<b>Major</b>	Beam angle	Yes	Unshared <sup>a</sup>
	Tube potential (kV)	Yes	Unshared <sup>a</sup>
	Added filtration (mm Cu)	Yes	Unshared <sup>a</sup>
	Organ shape/size	Not currently	Unshared
	Fat distribution	Not currently	Unshared
	X-ray field centring point	Yes (2 or more centres)	Unshared <sup>a</sup>
	X-ray field size	Yes (2 or more sizes)	Unshared <sup>a</sup>
<b>Moderate</b>	Use of lung shuttering	Potentially	Unshared <sup>a</sup>
	Level of inspiration	No	Unshared
	Contrast agent use	Potentially	Unshared <sup>a</sup>
	Field rotation	No	Unshared
	Inherent filtration (mm Al)	No	Shared <sup>b</sup>
<b>Minor</b>	Anode angle (degrees)	No	Shared <sup>b</sup>
	Voltage ripple	No	Shared <sup>b</sup>
	Table/mattress attenuation	Yes	Shared <sup>b</sup>
	Presence of ultrasound probe y/n	No	Unshared
	Monte Carlo errors <sup>c</sup>	No	Shared

<sup>a</sup>Some element of shared uncertainty, e.g. beam angles are relatively standardised for same procedure type.

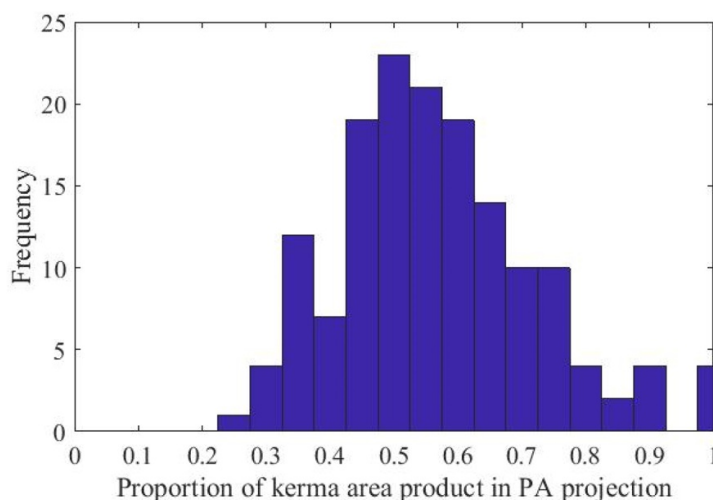
<sup>b</sup>Shared for same equipment.

<sup>c</sup>Arising from errors in interaction cross section and finite number of simulated particles. Shared for same Monte Carlo code with the same cross section library.

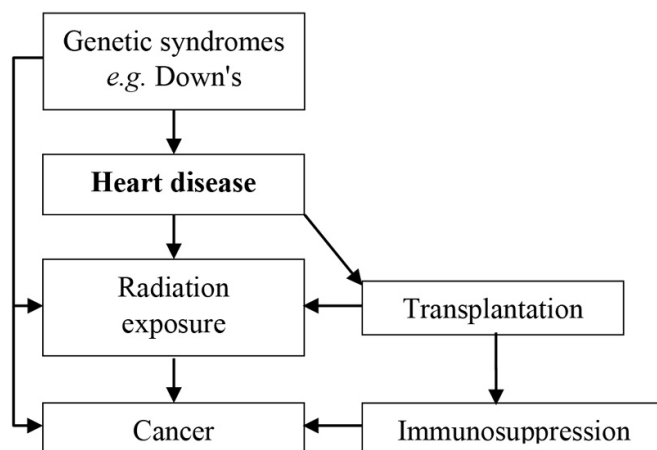
PDFs for input parameters will be based on the sample of radiation dose structured reports discussed above. For pre-RDSR era examinations, for which detailed exposure data are not available, PDFs will be wider, reflecting greater uncertainty. 2DMC methods have been applied to studies of radiation doses from CT [42] occupational exposures [43] and environmental exposures [44, 45] but not paediatric cardiac fluoroscopy, where information on uncertainties in dose estimates is currently very limited.

#### 2.4. Physical verification

We will verify the results of Monte Carlo simulations using measurements in physical anthropomorphic phantoms for a limited range of conditions. Measurements will be performed using LiF:Mg, Ti thermoluminescent dosimeters placed in RANDO-Alderson type anthropomorphic phantoms representing paediatric patients of a range of ages (new born, 1 year, 5 years and 15 years) [46] and adults. All phantoms include artificial skeletons, soft and lung tissues. Holes for TLDs are drilled in positions representing 19 internal organs. We will irradiate these phantoms using fluoroscopy equipment representative of the study period. In the event of discrepancy between physical and Monte Carlo results, we will perform Monte Carlo simulations using computational versions of the respective physical phantoms, voxelised from CT images. This will allow us to determine if discrepancies between physical and Monte Carlo methods are related to differences in phantom anatomy or the real/simulated x-ray beam.



**Figure 1.** Histogram of the proportion of kerma area product in the posterior-anterior (PA) projection for 154 pulmonary valvuloplasty procedures at a UK hospital [12]. In the 2DMC method, where the true beam angles are unknown, dose would be estimated multiple times (usually 200). For each of these ‘realisations’ the proportion of total  $P_{KA}$  in the PA projection would be sampled from a probability distribution based on these data. In this case, a PA proportion of around 0.5 would be sampled more often than other proportions.



**Figure 2.** Relationship between heart disease, radiation exposure, transplantation and cancer.

2.5. Epidemiological analysis

Cohort members will be followed-up using respective regional or national registries of vital status and cancer. The insurance data used to create the German cohort will also be used to obtain cancer diagnoses, except where data are obtained directly from hospitals, in which

national childhood cancer registry data will be used. In Italy, the cohort will be followed up directly using clinical records. Study entry will be the date of first cardiac fluoroscopy procedure. Doses will be lagged by two years for haematological malignancies and five years for all other malignancies. This takes the apparent minimum latency period for radiation induced cancer into account. The end point will be end of follow-up period, date of cancer diagnosis or date of death, whichever is sooner. Assuming national cohorts are evenly distributed throughout the respective data collection period, with a mean age at entry of 3 years, we expect approximately 50 cases of leukaemia and 37 lymphomas developing after the 2 year lag period, based on UK background rates [47, 48]. In reality, there are likely to be many more cases, due to the relatively high prevalence of predisposing factors to cancer in this population (discussed below).

We will perform a dose response analysis using appropriate regression modelling (either Cox or Poisson, to be decided), with dose treated as a time dependent variable. Methods to fully utilise 2DMC dose estimates are being developed [45] though with currently limited application to medical exposures. As a starting point, dose response analysis will be performed using the mean of the 2DMC realisations, followed by a sensitivity analysis using median and other percentiles. More advanced methods of incorporating 2DMC results will be adopted, where appropriate.

Evidence suggests radiation induced cancer tends to occur at the ages at which it normally occurs in the general population (e.g. [49]). While the lungs, breasts and oesophagus receive the highest organ doses in cardiac fluoroscopy [12, 13, 17], the follow-up during the HARMONIC study period (up to 2024) will be too short to allow sufficient cancers of these sites to accrue. Instead, we will initially focus on leukaemia and lymphoma, which are relatively common malignancies in early life [50]. Analysis for other sites, including thyroid and breast cancer will be considered as follow-up increases.

*Challenge 4.* Patients with congenital heart disease (CHD) are known to be at increased risk of cancer [23–25, 51]. Explanations include shared genetic and environmental risk factors, altered blood flow and hypoxia resulting from the disease itself or surgery such as Fontan's procedure [52, 53], as well as radiation exposure. If the underlying disease is associated with both increased risk of cancer and increased radiation exposure, the dose/risk relationship may be confounded (Figure 2). Down syndrome, for example, is associated with both heart disease and an increased risk of developing leukaemia [54].

A small proportion of individuals with congenital or acquired heart disease require a transplant, usually the heart itself, though occasionally heart and lungs. Transplantation, with associated immunosuppression, is a major risk factor for development of several cancer types [55], creating the potential for confounding of results.

*Proposed solution.* Wherever possible, each national cohort will be linked to a respective regional transplant registry to identify who has received a transplanted organ, the organ involved and date of transplant.

The impact of transplantation on apparent cancer risks in this patient group is potentially severe. In the previous UK cardiac catheterisation study [22], around 5% of cohort members were identified as transplant recipients. All lymphoma cases ( $n = 22$ ) developed in this group, post-transplant. Efforts to identify transplant recipients in the HARMONIC cohort are therefore essential. Transplant registries will be the primary source of information in the UK, Belgium and Spain. Information on transplant status will be obtained from the Patient Discharge Registry in Norway and from the Health Insurance records in France and Germany.

The relationship between radiation, transplant and cancer risk in this patient group is complex [56]. Individuals with the most severe forms of heart disease may require more x-ray procedures as part of their management, and have an increased need for transplant. In addition to drug-induced immunosuppression, transplant recipients also undergo regular radiological procedures to monitor the allograft for signs of rejection or vasculopathy, including coronary angiography and endomyocardial heart biopsy. Simply censoring transplant recipients, post-transplant, may also censor much of the dose received by these individuals [56]. In the case for the previous UK cardiac catheterisation study [22], the bulk of the radiation dose received by transplant patients did indeed appear to be post-transplant. The complex relationship between pre- and post-transplant radiation dose, immunosuppression and cancer risk must be analysed in detail, especially if the results are to be generalised, i.e. to all individuals exposed to radiation. As with dose, transplantation status will be included as a time-dependent variable in regression models.

### 3. Discussion

The sample size needed to precisely estimate the excess cancer risk from exposure to ionising radiation is inversely proportional to the square of the dose [57]. As doses approach the levels typical of diagnostic x-ray examinations or occupational exposures ( $< \approx 10$  mGy), the required sample sizes become so large that national and multinational pooled cohorts are generally required (e.g. [28, 58, 59]). The HARMONIC project is the latest of such efforts, potentially involving a combined cohort size ten times larger than any previous epidemiological analysis of radiation risks in this patient group. Clinicians, patients, parents and carers will benefit from improved information on the potential radiation related risks from cardiac fluoroscopy. This will aid the process of justification, balancing the benefits of the procedure with potential risks and comparing with alternatives such as surgery. Results will also aid optimisation of procedures through analysis of factors influencing dose such as frame rate, exposure factors and antiscatter grid usage. Reference dose levels can play an important role in radiation protection for cardiac fluoroscopy [60, 61, 64, 65]. Our data will allow the setting of reference doses, based on kerma area product or air kerma at the reference point. These will be set for individual procedure types defined in consultation with cardiologists.

The study has some important limitations. Firstly, even a combined cohort size of 100 000 may be insufficient to detect small cancer risks from cardiac fluoroscopy, especially from rare cancers. We should, however, be in the position to set an upper limit on potential risks and address concerns that risks may be especially high (e.g. [19]). Secondly, cancers of the organs receiving the highest doses from cardiac fluoroscopy (lungs, breasts, oesophagus) are predominantly diseases of middle and old age [50]. Incidence of these cancers is likely to be too small to allow meaningful analysis, even for countries with relatively long follow-up. Instead, risk projection methodologies could be used to estimate cancer risks in these organs, based on dose/risk relationships derived from other exposures (e.g. [26]). Uncertainties in dose estimates are likely to be large for early examinations (pre-2000) in which information on exposure parameters is limited. Uncertainties for examinations without associated dose indicators ( $P_{KA}$  or FT) will be especially large.

In spite of these limitations, the cardiac component of HARMONIC will provide unprecedented information on the radiation doses, past and present, from cardiac fluoroscopy in young people and provide important information to stakeholders on the potential associated cancer risks.



## Conflicts of interest

All authors declare they have no conflict of interest.

## Funding

The HARMONIC project (Health effects of cArDiac fluoRoscOpy and MOderN radIotherapy in paediatricS) has received funding from the Euratom research and training programme 2014–2018 under grant agreement No. 847707, and the British Heart Foundation.

## ORCID iDs

Richard W Harbron  <https://orcid.org/0000-0001-6073-2850>  
Isabelle Thierry-Chef  <https://orcid.org/0000-0001-6304-2783>  
Mark S Pearce  <https://orcid.org/0000-0002-0583-3779>  
Marie-Odile Bernier  <https://orcid.org/0000-0001-5807-4596>  
Serge Dreuil  <https://orcid.org/0000-0002-6160-0670>  
Estelle Rage  <https://orcid.org/0000-0002-3251-4124>  
Maria Grazia Andreassi  <https://orcid.org/0000-0002-2163-0816>  
Eugenio Picano  <https://orcid.org/0000-0002-6375-6361>  
Steffen Dreger  <https://orcid.org/0000-0001-7278-4789>  
Hajo Zeeb  <https://orcid.org/0000-0001-7509-242X>  
Hilde Olerud  <https://orcid.org/0000-0002-4940-7130>  
Utheya Thevathas  <https://orcid.org/0000-0001-8627-4413>  
Kristina Kjaerheim  <https://orcid.org/0000-0003-0691-3735>  
Andreas Jahnen  <https://orcid.org/0000-0002-7379-5145>  
Johannes Hermen  <https://orcid.org/0000-0002-1198-5701>  
Vadim Chumak  <https://orcid.org/0000-0001-6045-9356>  
Elena Bakhanova  <https://orcid.org/0000-0003-3960-5069>  
Vitalii Voloskyi  <https://orcid.org/0000-0002-9520-6372>  
David Borrego  <https://orcid.org/0000-0001-9868-5113>  
Choonsik Lee  <https://orcid.org/0000-0003-4289-9870>  
Jérémie Dabin  <https://orcid.org/0000-0002-9462-5807>

## References

- [1] Knowles R L, Bull C., Wren C, Wade A, Goldstein H and Dezateux C 2014 Modelling survival and mortality risk to 15 years of age for a national cohort of children with serious congenital heart defects diagnosed in infancy *PLoS One* **9** e106806
- [2] Stout K K *et al* 2019 2018 AHA/ACC guideline for the management of adults with congenital heart disease: a report of the American college of cardiology/American heart association task force on clinical practice guidelines *J. Am. Coll. Cardiol.* **73** e81–e192
- [3] Baumgartner H *et al* 2010 ESC guidelines for the management of grown-up congenital heart disease (new version 2010) *Eur. Heart J.* **31** 2915–57
- [4] Ait-Ali L, Andreassi M G, Foffa I, Spadoni I, Vano E and Picano E 2010 Cumulative patient effective dose and acute radiation-induced chromosomal DNA damage in children with congenital heart disease *Heart* **96** 269–74
- [5] Glatz A C, Purrington K S, Klinger A, King A R, Hellinger J, Zhu X, Gruber S B and Gruber P J 2014 Cumulative exposure to medical radiation for children requiring surgery for congenital heart disease *J. Pediatr.* **164** 789–794.e10

- [6] Johnson J N, Hornik C P, Li J S, Benjamin D K, Yoshizumi T T, Reiman R E, Frush D P and Hill K D 2014 Cumulative radiation exposure and cancer risk estimation in children with heart disease *Circulation* **130** 161–7
- [7] Ozasa K, Shimizu Y, Suyama A, Kasagi F, Soda M, Grant E J, Sakata R, Sugiyama H and Kodama K 2012 Studies of the mortality of atomic bomb survivors, report 14, 1950–2003: an overview of cancer and noncancer diseases *Radiat. Res.* **177** 229–43
- [8] Clement C H *et al* 2012 ICRP publication 118: ICRP statement on tissue reactions and early and late effects of radiation in normal tissues and organs—threshold doses for tissue reactions in a radiation protection context *Ann. ICRP* **41** 1–322
- [9] Shore R E *et al* 2018 Implications of recent epidemiologic studies for the linear nonthreshold model and radiation protection *J. Radiol. Prot.* **38** 1217–33
- [10] UNSCEAR Sources 2013 *Effects and Risks of Ionising Radiation, Annex B: Effects of Radiation Exposure of Children* (New York: United Nations)
- [11] National Institute for Cardiovascular Outcomes Research (NICOR) 2019 *National Congenital Heart Disease Audit 2019 Summary Report* (available at: [www.nicor.org.uk/wp-content/uploads/2019/09/NCHDA-2019-Summary-Report-final.pdf#page=6](http://www.nicor.org.uk/wp-content/uploads/2019/09/NCHDA-2019-Summary-Report-final.pdf#page=6))
- [12] Harbron R W, Pearce M S, Salotti J A, McHugh K, McLaren C, Abernethy L, Reed S, O'sullivan J and Chapple C L 2015 Radiation doses from fluoroscopically guided cardiac catheterization procedures in children and young adults in the United Kingdom: a multicentre study *Br. J. Radiol.* **88** 20140852
- [13] Yakoumakis E, Kostopoulou H, Makri T, Dimitriadis A, Georgiou E and Tsalafoutas I 2013 Estimation of radiation dose and risk to children undergoing cardiac catheterization for the treatment of a congenital heart disease using Monte Carlo simulations *Pediatr. Radiol.* **43** 339–46
- [14] Karambatsakidou A, Steiner K, Fransson A and Poludniowski G 2020 Age-specific and gender-specific radiation risks in paediatric angiography and interventional cardiology: conversion coefficients and risk reference values *Br. J. Radiol.* **93** 20190869
- [15] Journy N *et al* 2018 Projected future cancer risks in children treated with fluoroscopy-guided cardiac catheterization procedures *Circ. Cardiovasc. Interv.* **11** 1–9
- [16] Ubeda C, Salazar L, Retana V, Gutierrez R, Nocetti D and Reyes C 2019 Organ doses in paediatric interventional cardiology. First values for patients in Costa Rica *Radiat. Phys. Chem.* **162** 48–53
- [17] Jones T P, Brennan P C and Ryan E 2017 Cumulative effective and individual organ dose levels in paediatric patients undergoing multiple catheterisations for congenital heart disease *Radiat. Prot. Dosim.* **176** 252–7
- [18] Spengler R F, Cook D H, Clarke E A, Olley P M and Newman A M 1983 Cancer mortality following cardiac catheterization: a preliminary follow-up study on 4,891 irradiated children *Pediatrics* **71** 235–9
- [19] Stern S, Hapfelmeier M, Naumann S and Spix E 2020 Increased cancer incidence following up to 15 years after cardiac catheterization in infants under one year between 1980 and 1998—a single center observational study *J. Clin. Med.* **9** 315
- [20] McLaughlin J, Kreiger N, Sloan M P, Benson L N, Hilditch S and Clarke E A 1993 An historical cohort study of cardiac catheterization during childhood and the risk of cancer *Int. J. Epidemiol.* **22** 584–91
- [21] Modan B, Keinan L, Blumstein T and Sadetzki S 2000 Cancer following cardiac catheterization in childhood *Int. J. Epidemiol.* **29** 424–8
- [22] Harbron R W, Chapple C-L, O'Sullivan J J, Lee C, McHugh K, Higuera M and Pearce M S 2018 Cancer incidence among children and young adults who have undergone x-ray guided cardiac catheterization procedures *Eur. J. Epidemiol.* **33** 393–401
- [23] Cohen S, Liu A, Gurvitz M, Guo L, Therrien J, Laprise C, Kaufman J S, Abrahamowicz M and Marelli A J 2018 Exposure to low-dose ionizing radiation from cardiac procedures and malignancy risk in adults with congenital heart disease *Circulation* **137** 1334–45
- [24] Bjørge T, Cnattingius S, Lie R T, Tretli S and Engeland A 2008 Cancer risk in children with birth defects and in their families: A population based cohort study of 5.2 million children from Norway and Sweden *Cancer Epidemiol. Biomark. Prev.* **17** 500–6
- [25] Mandalenakis Z, Karazisi C, Skoglund K, Rosengren A, Lappas G, Eriksson P and Dellborg M 2019 Risk of cancer among children and young adults with congenital heart disease compared with healthy controls *JAMA Netw. Open* **2** 1–9
- [26] National Research Council 2006 *Health Risks from Exposure to Low Levels of Ionizing Radiation: BEIR VII Phase 2* (Washington, DC: National Academies Press)

- [27] Calabrese E J and O'Connor M K 2014 Estimating risk of low radiation doses—a critical review of the BEIR VII report and its use of the linear no-threshold (LNT) hypothesis *Radiat. Res.* **182** 463–74
- [28] De Basea M B *et al* 2015 EPI-CT: design, challenges and epidemiological methods of an international study on cancer risk after paediatric and young adult CT *J. Radiol. Prot.* **35** 611–28
- [29] Baysson H, Réhel J L, Boudjemline Y, Petit J, Girodon B, Aubert B, Laurier D, Bonnet D and Bernier M O 2013 Risk of cancer associated with cardiac catheterization procedures during childhood: A cohort study in France *BMC Public Health* **13** 1–8
- [30] De González A B *et al* 2016 Relationship between paediatric CT scans and subsequent risk of leukaemia and brain tumours: assessment of the impact of underlying conditions *Br. J. Cancer* **114** 388–94
- [31] Journy N, Rehel J L, Le Pointe H D, Lee C, Brisse H, Chateil J F, Caer-Lorho S, Laurier D and Bernier M O 2015 Are the studies on cancer risk from CT scans biased by indication? Elements of answer from a large-scale cohort study in France *Br. J. Cancer* **112** 185–93
- [32] Lee C, Kim K P, Bolch W E, Moroz B E and Folio L 2015 NCICT: a computational solution to estimate organ doses for pediatric and adult patients undergoing CT scans *J. Radiol. Prot.* **35** 891–909
- [33] Kramer R, Khoury H J and Vieira J W 2008 CALDose\_X—a software tool for the assessment of organ and tissue absorbed doses, effective dose and cancer risks in diagnostic radiology *Phys. Med. Biol.* **53** 6437–59
- [34] Harbron R W, Pearce M S and Chapple C 2018 CD16: a MATLAB-based application for estimating radiation doses from x-ray guided cardiac catheterizations in children arXiv:1807.05823
- [35] Pelowitz D 2011 *MCNPX User's Manual, Version 2.7.0, Los Alamos National Laboratory Report LA-CP-11-00438*
- [36] Bolch W E *et al* n.d. Paediatric reference computational phantoms *Ann. ICRP*, ed C H Clement and H Fujita
- [37] Digital Imaging and Communication in Medicine (DICOM) *Radiation Dose Recording* [www.dicomstandard.org/using/radiation/](http://www.dicomstandard.org/using/radiation/) (Accessed 3 April 2020)
- [38] OpenREM *Free and Open Source Radiation Exposure Monitoring for the Physicist* <https://openrem.org/> (Accessed 17 March 2020)
- [39] Villoing D and Lee C 2019 NCINM: a computational phantom-based dosimetry tool for patients undergoing nuclear medicine procedures *J. Nucl. Med.* **60** 1634
- [40] Hofer E 2008 How to account for uncertainty due to measurement errors in an uncertainty analysis using Monte Carlo simulation *Health Phys.* **95** 277–90
- [41] Simon S, Hoffman F and Hofer E 2015 The two-dimensional Monte Carlo: a new methodologic paradigm for dose reconstruction for epidemiological studies *Radiat. Res.* **183** 27–41
- [42] Lee C, Journy N, Moroz B E, Little M, Harbron R, McHugh K, Pearce M and De Gonzalez A B 2019 Organ dose estimation accounting for uncertainty for pediatric and young adult ct scans in the United Kingdom *Radiat. Prot. Dosim.* **184** 44–53
- [43] Hoffmann S, Laurier D, Rage E, Guihenneuc C and Ancelet S 2018 Shared and unshared exposure measurement error in occupational cohort studies and their effects on statistical inference in proportional hazards models *PLoS One* **13** 1–22
- [44] Land C E, Kwon D, Hoffman F O, Moroz B, Drozdovitch V, Bouville A, Beck H, Luckyanov N, Weinstock R M and Simon S L 2015 Accounting for shared and unshared dosimetric uncertainties in the dose response for ultrasound-detected thyroid nodules after exposure to radioactive fallout *Radiat. Res.* **183** 159
- [45] Wu Y, Hoffman F O, Apostoaei A I, Kwon D, Thomas B A, Glass R and Zablotska L B 2019 Methods to account for uncertainties in exposure assessment in studies of environmental exposures *Environ. Health* **18** 1–15
- [46] Varchena V 2002 Pediatric phantoms *Pediatr. Radiol.* **32** 280–4
- [47] Cancer Research UK Non-Hodgkin lymphoma incidence statistics [www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/non-hodgkin-lymphoma/incidence#heading-One](http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/non-hodgkin-lymphoma/incidence#heading-One) (Accessed 10 March 2020)
- [48] Cancer Research UK Hodgkin lymphoma incidence statistics [www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/hodgkin-lymphoma/incidence](http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/hodgkin-lymphoma/incidence) (Accessed 5 March 2020)
- [49] Preston D L, Ron E, Tokuoka S, Funamoto S, Nishi N, Soda M, Mabuchi K and Kodama K 2007 Solid cancer incidence in atomic bomb survivors: 1958–1998 *Radiat. Res.* **168** 1–64

- [50] Forman D, Bray F, Brewster D H, Gombe Mbalawa C, Kohler B, Piñeros M, Steliarova-Foucher E, Swaminathan R and Ferlay J eds 2016 *Cancer Incidence in Five Continents* vol X (Lyon: International Agency for Research on Cancer)
- [51] Collins R T, Von Behren J, Yang W, Carmichael S L, Reynolds P, Fisher P G and Shaw G M 2018 Congenital heart disease complexity and childhood cancer risk *Birth Defects Res.* **110** 1314–21
- [52] Egbe A C *et al* 2018 Hepatocellular carcinoma after Fontan operation: multicenter case series *Circulation* **138** 746–8
- [53] Agarwal S, Jindal I, Balazs A and Paul D 2019 Catecholamine-secreting tumors in pediatric patients with cyanotic congenital heart disease *J. Endocr. Soc.* **3** 2135–50
- [54] Hasle H, Haunstrup Clemmensen I and Mikkelsen M 2000 Risks of leukaemia and solid tumours in individuals with Down's syndrome *Lancet* **355** 165–9
- [55] Grulich A E, van Leeuwen M T, Falster M O and Vajdic C M 2007 Incidence of cancers in people with HIV/AIDS compared with immunosuppressed transplant recipients: a meta-analysis *Lancet* **370** 59–67
- [56] Richardson D B and Keil A P 2018 Challenges to studying population effects of medical treatments *Eur. J. Epidemiol.* **33** 365–8
- [57] Land C E 1981 Statistical limitations in relation to sample size *Environ. Health Perspect.* **42** 15–21
- [58] Gillies M *et al* 2017 Mortality from circulatory diseases and other non-cancer outcomes among nuclear workers in France, the United Kingdom and the United States (INWORKS) *Radiat. Res.* **188** 276
- [59] Dauer L T, Woods M, Miodownik D, Serencsits B, Quinn B, Bellamy M, Yoder C, Liang X, Boice J D J and Bernstein J 2019 Cohort profile—MSK radiation workers: a feasibility study to establish a deceased worker sub-cohort as part of a multicenter medical radiation worker component in the million person study of Low-Dose radiation health effects *Int. J. Radiat. Biol.* **1–7**
- [60] Kobayashi D *et al* 2014 Standardizing radiation dose reporting in the pediatric cardiac catheterization laboratory—a multicenter study by the CCISC (congenital cardiovascular interventional study consortium) *Catheter. Cardiovasc. Interv.* **84** 786–93
- [61] Quinn B P *et al* 2020 Longitudinal improvements in radiation exposure in cardiac catheterization for congenital heart disease: a prospective multicenter C3PO-QI study *Circ. Cardiovasc. Interv.* **13** e008172
- [62] Lee Y S *et al* 2015 The risk of cancer in patients with congenital heart disease: a nationwide population-based cohort study in Taiwan *PLoS One* **10** 1–13
- [63] Krille L *et al* 2015 Risk of cancer incidence before the age of 15 years after exposure to ionising radiation from computed tomography: results from a German cohort study *Radiat. Environ. Biophys.* **54** 1–12
- [64] Glatz A C, Patel A, Zhu X, Dori Y, Hanna B D, Gillespie M J and Rome J J 2014 Patient radiation exposure in a modern, large-volume, pediatric cardiac catheterization laboratory *Pediatr. Cardiol.* **35** 870–8
- [65] Cevallos P C, Armstrong A K, Glatz A C, Goldstein B H, Gudausky T M, Leahy R A, Petit C J, Shahanavaz S, Trucco S M and Bergersen L J 2017 Radiation dose benchmarks in pediatric cardiac catheterization: a prospective multi-center C3PO-QI study *Catheter. Cardiovasc. Interv.* **90** 269–80