POLICY BRIEF

Harmonic

Health effects of cardiac fluoroscopy and modern radiotherapy in paediatrics

Objective This **policy brief** is a call to funders, hospitals, ethical committees, and vital status and cancer registry authorities to provide the necessary legal, technical and financial support for the long-term follow-up of paediatric patients exposed to ionising radiation (e.g. radiotherapy) in Europe. Without this support, vital opportunities to advance our understanding of radiation-related health risks and protect children and other vulnerable populations will be lost.

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Introduction

The **long-term follow-up of paediatric patients exposed to ionising radiation** is critical for understanding and mitigating the potential health risks these individuals face later in life. However, researchers are frequently confronted with **three major barriers** when conducting this kind of epidemiological studies:

i) Collecting/accessing individual patient data: Data collection requires manpower and digital expertise, and the process may vary between hospitals, leading to some inconsistencies. Additionally, hospital image repositories frequently contain incomplete data, which hinders accurate dose reconstruction and limits their potential to generate robust scientific evidence.

ii) Linking patient data with national disease and vital status registries: Disease registries, designed for public health surveillance, are crucial for tracking health outcomes. They store comprehensive data on patient demographics, disease characteristics, treatments, and outcomes, while maintaining strict confidentiality standards. Barriers in linking patient data with cancer registries limit the ability to obtain complete datasets, thereby affecting the quality of the analyses and the robustness of the results.

iii) Sharing data between countries: Investigating the health effects of exposure to low-dose radiation requires pooling data from various centres and countries to reach statistical significance and ensure the reliability of the results. For many European research projects, the recent implementation of the General Data Protection Regulation (GDPR) has added complexity to the process of data sharing between partners and across countries. This is largely due to variations in how different countries and institutions interpret and implement the regulation.

The HARMONIC experience

The European-funded **HARMONIC project** aimed to understand the long-term health effects of medical radiation exposure in children, particularly those undergoing radiotherapy for cancer or X-ray guided cardiac interventions. One of its main achievements was to establish the infrastructure for the long-term follow-up of two patient cohorts: **cancer patients** treated with modern radiotherapy techniques, and **cardiac patients** treated with X-ray guided procedures.
Here, we share some of the challenges and possible solutions when establishing these databases, linking them to disease registries, and sharing them between partners.

"Our ultimate goal is to improve the quality of life of children treated with medical radiation"

harmonicproject.eu

1 Collecting and accessing data

Specific challenges

The quality of data: The two HARMONIC cohorts have their own specificities in terms of data collection. For the cardiac patient cohort, data are primarily collected retrospectively and without intervention, except for a small group that provided biological samples. In contrast, the cancer patient cohort incorporates both retrospective and prospective data collection, with some patients participating in specific research activities that involve additional interventions, such as MRI sequences, blood sampling and quality of life surveys. The quality of the data varies on whether it is collected prospectively – where the project defined the level of details - or retrospectively retrieved from hospital archives. Striking the right balance between gathering sufficient information to conduct robust analyses and the effort required to extract this data is fundamental to ensure exhaustivity of the database.

Extracting necessary radiation and imaging data from records. Accurate estimation of radiation doses received by specific organs during diagnosis and treatment is essential for analysing health outcomes in both HARMONIC cohorts. This process heavily relies on the extraction of detailed technical information from imaging and radiation treatment data. The relatively recent implementation of the DICOM (Digital Imaging and COmmunications in Medicine) system has facilitated the archiving and retrieval of individual procedure data. However, many records are stored in PACS (Picture Archiving and Communication Systems), which can differ widely between providers and require specialised expertise to effectively extract the data. We also found that in some cases, even when the PACS or a specific collection software was available, it was not properly connected to the equipment used in the paediatric departments.

Solutions

Close interaction with clinical teams. By integrating the clinical teams, particularly in the oncology and cardiology departments, as partners in the research project, we established a strong collaborative framework. This facilitated both data access and regular communication to define the necessary parameters for collection. As a result, we ensured that all relevant demographic, clinical, radiological, dosimetric, biological and social data were available for analysis. We also maintained contact with medical physicists from the participating hospitals to obtain information on the more technical aspects of dose reconstruction, addressing missing parameters or uncertainties.

Special software. In the HARMONIC project, we implemented a series of strategies to gather the necessary dosimetric data. In hospitals where PACS data extraction software was unavailable, we provided DICOMInspector, a software solution developed within the project to facilitate data collection and PACS data extraction. Beyond data collection, DICOMINspector offers a range of useful options for further analyses of PACS data.

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Linking data to national disease registries

Specific challenges

Explicit informed consent. A key barrier to linking individual data to national disease registries is the requirement by some institutions for the patient's explicit informed consent. In particular, some local ethics committees were reluctant to authorise the transfer of non-anonymised data from hospitals to cancer registries without obtaining individual consent. While informing patients about the use of their data is a fundamental ethical principle, obtaining this consent retrospectively - especially for treatments that took place years ago - poses significant challenges and often requires an unreasonable amount of effort.

When the patients are children, these challenges are further amplified. Paediatric cohorts require special ethical considerations, including the need for informed consent from both their legal representatives and the children themselves when they reach the appropriate age for decision making (assent). Specific consent documents, adapted in language and format, need to be developed to ensure that the patients and their legal representatives fully understand the purpose of the research, who has access to the data and where and how it is stored, and their right to withdraw from the study at any time. Requesting informed consent from parents for the use of these data in a new study can cause anxiety in the families, or great distress in cases where the child has died.

Solutions

Exemptions. In HARMONIC, we were able to obtain an exemption of individual informed consent in certain cases of observational research on collected treatment and outcome data, specifically in the following situations:

- For deceased patients, where it is not possible to obtain consent but their inclusion in the analyses remains essential.
- For very large cohorts, such as in epidemiological studies on the effects of exposure to low doses of ionising radiation, where contacting all participants is unfeasible, especially if they have changed address or no longer attend the participating hospital, as is often the case with paediatric hospitals.

We made sure that collective information on the study, its objectives and the responsible parties were easily accessible in participating hospitals and on the project's website. This allows patients the option to withdraw from the study at any time.

3 Sharing data between countries

Specific challenges

Delays. While there is no official legal barrier to sharing data between European countries, HARMONIC faced considerable delays in obtaining the necessary agreements between legal teams from multiple countries and institutions.

Transfer of sensitive data. Long-term follow-up of patients requires keeping the ID of the patient for linkage with disease and vital status registries. Data is therefore pseudonymised before sharing with the research team, and the patient's identity is kept in a secured file with restricted access. In our experience, this process cannot always be assured within the institution providing the data but has to be implemented by a third party.

Solutions

Meetings with legal teams. For the radiotherapy cohort, the overall legal framework was extensively discussed between legal officers before drafting an agreement whereby they were collectively responsible for the data. Given that exchange through emails was highly unproductive, we organised online meetings with and between lawyers to facilitate discussions.

A GDPR-compliant software. For the cardiology cohort, our strategy was to set-up the use of a GDPR-compliant software that enables the remote and non-disclosive analysis of sensitive research data (DataSHIELD). The data to be analysed can remain in the primary investigating institution, assuming the same structure is used in all participating institutions, thereby preventing the transfer and storage of data in a single centralised database.

Recommendations

1. Continue to work on the **standardisation of a comprehensive imaging data repository**, which has the potential to provide all necessary parameters for organ dose reconstruction. *Who: Health authorities, professional associations together with manufacturers.*

2. Ensure **efficient communication with ethical committees and Data Protection Officers** (DPOs) to agree on conditions under which exemption of individual informed consent is possible. *Who: PIs, DPOs and ethical committees.*

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3. **Involve lawyers and DPOs** from participating institutions and registries from the early stages of the project proposal to avoid delays in data sharing. *Who: project leaders and managers.*

4. **Share data on secured well-designed platforms** such as DataSHIELD to avoid the transfer and disclosure of sensitive data between institutions and countries. *Who: PIs and platform developers.*

5. Provide adequate **funding** to ensure **long-term sustainability of disease registries**, which are critical for advancing epidemiological research and informing public health measures. *Who: European bodies, national authorities.*

Final remarks

The cohort databases established by the HARMONIC project hold significant potential beyond the project's lifespan, as many cancer and non-cancer late effects take years to manifest and can only be identified with large patient numbers. We have a responsibility – both to patients and funders - to fully use these resources by expanding them to other centres and enabling future studies on potential late effects.

Ensuring the longevity of these databases demands not only sustained funding but also the establishment of robust legal and technical frameworks. We expect the implementation of the recently approved European Health Data Space to be an important step towards facilitating the use of health data for research, innovation and public health purposes.

Only through coordinated efforts from healthcare providers, health authorities, researchers, funders, and policymakers can we unlock the full potential of these invaluable resources and continue to advance our understanding of radiation risks.