MEDIRAD

RECOMMENDATIONS TO ENHANCE THE EFFECTIVE PROTECTION OF PATIENTS AND MEDICAL PROFESSIONALS, AND TO IDENTIFY FURTHER RESEARCH PRIORITIES

PROJECT TITLE

Implications of Medical Low Dose Radiation Exposure

This project has received funding from the Euratom research and training programme 2014–2018 under grant agreement No 755523.

For more information: **www.medirad-project.eu**

About MEDIRAD Recommendations

MEDIRAD is a research project funded by EURATOM under Horizon 2020 Programme (2016/ 2022). Bringing together radiological and clinical research teams from several European countries, it aimed to enhance the scientific basis and clinical practice of radiation protection in the medical field, in particular by better understanding and evaluating the health effects of exposure to low doses of ionising radiation resulting from diagnostic and therapeutic applications. MEDIRAD was designed to have direct implications for the radiological safety of European patients undergoing medical imaging and therapy procedures involving ionising radiation, and of exposed medical professionals. For this purpose, one of the goals of MEDIRAD was to establish evidence-based consensus policy recommendations for enhancing the effective protection of patients and medical professionals, as well as for identifying further research priorities.

The scientific basis for the following recommendation stems from the research developed in the course of the MEDIRAD project. In order to achieve a sufficient degree of consensus, MEDIRAD engaged in a substantial dialogue with relevant stakeholders in Europe and internationally. The MEDIRAD Stakeholder Forum, which underpinned this dialogue, included representatives from 86 organisations who were invited to express their views on issues to be considered as priority, and to comment on the draft formulation of MEDIRAD recommendations.

MEDIRAD Recommendations are made publicly available under the sole authority of the MEDIRAD Consortium. More information on MEDIRAD is available in Annex 3.

Competent international organisations, public authorities at European and national level, and organisations such as European research platforms and professional or patient associations, are invited to consider these recommendations and engage or support actions towards their implementation as they see fit, taking the opportunity of initiatives such as the SAMIRA (Strategic Agenda for Medical Ionising radiation Applications) European Action plan.

MEDIRAD

RECOMMENDATION 1

CONSOLIDATION OF PATIENT DATA REPOSITORIES ACROSS EUROPE

PROJECT TITLE

Implications of Medical Low Dose Radiation Exposure

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Introduction

Patient data repositories are an essential source of information both for optimising patient treatment and follow-up and for improving scientific understanding of effects of medical radiation exposure. This set of recommendations is based on the experience acquired through the MEDIRAD project (see Annex 1), and addresses two fundamental and challenging aspects related to the consolidation and use of patient data repositories across Europe: adequate storing of the data, the access to such data for research purposes in a manner that protects them according to current regulations (i.e. the General Data Protection Regulation).

Access to an organised collection of clinical image and dose data at the European level, suitably coded to effectively protect the patients' identities, is of utmost importance to advance radiation protection research, clinical practice, and personalised medicine. Such an infrastructure enables the collection, storage, and retrieval of image and dose data, together with essential clinical / patient data, offering a means by which to efficiently conduct large-scale multinational epidemiological studies, benchmark clinical practice, and optimise patient care through precision medicine [1]. Furthermore, image and dose data repositories are an essential resource for developing artificial intelligence (AI) solutions that hold the potential to revolutionise medical applications of ionising radiation, including medical imaging, nuclear medicine, radiotherapy, and integrated diagnostics [2]. The current unavailability of a robust and efficient interconnected system of repositories represents a major barrier to the clinical translation of ionising radiation research, which must be urgently addressed, a conclusion that is supported by the findings of a recent Delphi study conducted within the EURAMED Rocc-n-Roll project [3]. However, the creation and upkeep of such repositories is an expensive, resource intensive and lengthy investment, particularly given the heterogeneity of imported data and associated data sources [4].

Therefore, it would be greatly beneficial to develop an interconnected image and dose repository system at the European level, guaranteeing patient data protection, featuring standardised characterisation of data sets and which could be maintained over time and remain accessible for numerous research and innovation projects. Such a system could also have subsequent impact at the European and global level.

Biomedical and radiation protection research increasingly relies on personal data pertinent for the analysis of exposure / health effects associations. Access to and exploitation of such data is regulated by the General Data Protection Regulation (GDPR) Directive [5], which was implemented, with national variations between European countries, in 2018. Such variations present high difficulties for European research projects that require access to, and exploitation of, personal data across several countries (e.g. epidemiological studies, biobanks, dosimetric and imaging repositories, etc.). Efforts to harmonise regulatory practice should be encouraged, notably through the collection of experience gathered through EURATOM research projects. Other EU initiatives on GDPR implementation have been launched, including the European Health Data Space [6,7].

The MEDIRAD project started in June 2017, whereas the GDPR came into effect in 2018. Accordingly, the project had to adapt procedures involving utilisation of patient data for its scientific investigations. The objective of the following recommendations is to facilitate the development of large-scale multinational epidemiological studies, by proposing guidelines to help European countries implement European regulatory requirements on ethics (including compliance with GDPR Directive). Guidance should be available for helping research projects to manage the GDPR rules but should be regularly reviewed and improved to take into account lessons learnt, the evolution of regulatory practice in member states, and the developing jurisprudence at the European level.

1

European imaging and dose repositories.

Overall recommendation

Develop an interconnected and sustainable system of image and dose repositories at the European level.

» **Specific recommendations:**

1. Encourage the long-term development and maintenance of an interconnected system of key imaging and dose repositories.
2. Develop comprehensive guidelines for repository development, maintenance, and operation, in adherence with the framework and based on principles of data quality, robust and standardised infrastructure, and interoperability.
3. Support the development of European / international standards (coding schemes and structured reporting templates) for clinical practice.
4. Encourage the research community and practitioners to utilise structured data capture and reporting in medical imaging through European Commission based recommendations.
5. Support education and training initiatives to increase competency, harmonised implementation, and adherence to DICOM standards within industry.
6. Request transparency regarding the workings and dependencies of commercial tools.
7. Encourage the use of an application programming interface (API) in imaging and dose repositories and the continued development of meta-analysis tools to optimise data upload and analysis, respectively.
8. Encourage open-source repositories wherever manageable.
9. Encourage and support the interoperability of biobanks with image and dose data repositories, considering existing recommendations and infrastructure.

1.1. Justification

Within the MEDIRAD project a multinational, centralised, and integrated imaging and dose data repository, the Image and Radiation Dose BioBank or IRDBB, was constructed to support the research conducted across the project's 14 participating countries and research-centred work packages. More specifically, the repository was created as an integrated system comprised of both a DICOM data repository, suitable for managing radiological images and radiation dose structured reports, and a resource description framework (RDF) repository, supporting the semantic (i.e. ontology-based) descriptions of both DICOM and non-DICOM data, all accessible via optimised web-based application programming interfaces (API).

In this way, CT images and corresponding dosimetric data, along with associated metadata (demographics, clinical study descriptors, processing procedures, etc.) could be uploaded from multiple clinical studies and geographic locations for central storage, retrieval, and query with relative ease.

The MEDIRAD IRDBB thus provides proof-of-concept of an EU-wide repository for radiation research. Based on this experience, as detailed in Annex 1, the following science-based policy recommendations have been drawn in an effort to advocate and facilitate the further development of a European interconnected system of imaging and dose repositories for patients exposed to ionising radiation.

1.2. Implementation

1. Encourage the long-term development and maintenance of an interconnected system of key imaging and dose repositories.

Development and maintenance of imaging and dose repositories is a very resource intensive and costly investment, requiring an estimated €1-1.5 million per annum for their maintenance and growth; the upfront costs of constructing such an infrastructure can be even higher. As a means of exploiting the vast benefits of radiological repositories in a cost-effective and sustainable manner, it is recommended that an interconnected system of key imaging and dose repositories be set-up and maintained for years / decades as a critical research and development infrastructure accessible to research projects of all sizes throughout Europe.

Moreover, in order to avoid dispersion of efforts, it is recommended that existing repository initiatives be consolidated where practicable and linked with other repositories beyond the scope of ionising radiation research as part of the broader European Health Data Space for maximum impact [6].

To this end, a minimum 0.5% of Euratom annual research funding should be allocated to further developing, sustaining, and improving a robust and efficient repository network. In this way, the value of big data for clinical practice, epidemiological studies, AI / machine learning, quality control, and optimisation of patient care and follow-up (among other applications in medical radiation research) can be maximised while overhead costs are minimised.

» Target audience: Euratom authorities, public health authorities, medical professional organisations, research communities.

2. Develop comprehensive guidelines for repository development, maintenance, and operation, in adherence with the framework and based on principles of data quality, robust and standardised infrastructure, and interoperability.

The legal framework currently governing image and dose data repositories should be clearly outlined through a comprehensive central document with links to all relevant regulations and legislation (e.g. GDPR) to provide a central resource for repository developers, managers, and users, as well as the general public. Based on this, comprehensive guidelines should be developed for repository development, maintenance, and operation, promoting adherence to relevant regulations, legislation, international standards of practice, and the principles of the European Health Data Space [6].

These guidelines are to be developed in consultation with all actors (patients, industry, academia, etc.) involved in the development, maintenance and/or use of such repositories to ensure they address the needs of each group and effectively support them in overcoming barriers to regulatory adherence, high-quality data, standardised infrastructure, and information exchange. Of critical importance is the need for all repositories to have a quality assurance programme which ensures data sets meet quality requirements clearly specified within the legal framework and accompanying guidelines. Guidelines should also facilitate adherence to defined standards of practice and harmonised procedures where applicable. In this way, interoperability can be achieved, and the validity of associated research outputs / products better assured.

» Target audience: Euratom authorities, regulatory authorities.

3. Support the development of European / international standards (coding schemes and structured reporting templates) for clinical practice.

The successful implementation of an interconnected and sustainable system of imaging and dose data repositories, together with essential clinical / biological patient data, requires interdisciplinary cooperation and harmonisation efforts. It is crucial that radiation protection and clinical research teams across Europe work together through joint programming and research relevant to both parties in order to meet the urgent need for accessible, well organised, and representative big data. As we work towards increased standardisation for mass pooling of data sets, changes will be required. These changes must be accompanied by robust user-friendly tools that ease the burden on those involved at the operational level (e.g. clinicians), thereby facilitating the practical implementation and wide-spread adoption of such standards.

The main opportunities for cooperation and harmonisation are outlined below.

• Support / fund the development of improved coding schemes for clinical imaging procedures.

While current international standards, such as DICOM SR-concept and RadLex, provide solutions to much of the variability that exists in radiological reporting, there is an unmet need for increased precision when categorising imaging procedures, which could be achieved with a more comprehensive set of modifiers. To ensure the usefulness of repositories, a complete and standardised collection of procedural descriptors should be developed, frequently reviewed, and regularly updated by international organisations to allow for distinct aspects of radiological procedures, such as level of radiation (low-dose-protocol vs. standard-dose-protocol) and contrast phases (e.g., arterial / venous / late) to be reported in an internationally harmonised manner. The issue of imprecise categorisation is partly resolved by the LOINC/RSNA Radiology Playbook. However, a more exhaustive set of modifiers is required to reach the full potential of imaging and dose repositories. Thus, improved systems for categorising imaging procedures should be a priority item for inclusion in future research and development roadmaps. In parallel, software tools that facilitate implementation of the coding schemes into everyday clinical work-flows should be developed for maximum utility. Ideally, this would be coordinated at the EU or international level by organisations such as EURAMED, to best ensure harmonisation.

• Support / fund expert networks for the development of structured reporting templates for clinically relevant procedures.

The adoption by clinicians of structured reporting templates that incorporate standardised coding schemes is of critical importance for consolidating imaging and dose data repositories. Building upon the template developed in MEDIRAD, templates focused on a set of pertinent clinical procedures should be developed, frequently reviewed, and regularly updated by expert working groups led by pertinent scientific societies at the national, European, and international levels. Therefore, funding and support for European-based initiatives complementary to the RSNA RadReport Template Library is essential for the development of European-level repositories.

» Target audience: public health authorities, medical professional organisations, scientific communities, industry, clinicians, and practitioners.

4. Encourage the research community and practitioners to utilise structured data capture and reporting in clinical imaging through European Commission based recommendations.

Structured data capture and reporting will greatly facilitate the consolidation of Europe-wide data into large-scale registries. To this end, Euratom guidance documents will be needed to encourage their implementation. Furthermore, the quality and completeness of imaging / radio-therapy reports should be improved by future research and technology development programmes. Structured reporting should focus on a set of clinically relevant procedures (e.g. CT for pulmonary embolism, Cardiac-CT, oncological imaging, head and neck radiotherapy, thyroid ablation, etc.) to streamline implementation and use [8]. Where applicable, currently available international standards should be utilised and enforced.

These solutions include DICOM SR-concept, IHE MRRT profile, and SNOMED CT for general coding, as well as RadLex for radiology specific terms.

» Target audience: Euratom authorities, regulatory authorities, research community, practitioners.

5. Support education and training initiatives to increase competency, harmonised implementation, and adherence to DICOM standards within industry.

As the international standard for communication and management of medical imaging, DICOM is a cornerstone of information sharing in medical imaging and represents an essential element for creating the fully interoperable multi-vendor environment needed to develop, maintain, and use imaging repositories efficiently. Therefore, it is critical that all industry professionals / developers / manufacturers in the fields of diagnostic medical imaging, image-based therapies and associated research have a working knowledge of DICOM to assure interoperability between imaging / radiotherapy equipment and other systems, including repositories.

To this end, support to education and training initiatives that increase the competence of industry staff in this regard is highly recommended. Additionally, close collaboration between industry, academia, clinical practice, and the DICOM standards team should be encouraged, particularly when adapting standards to facilitate the incorporation of additional / novel data.

» Target audience: industry, medical professional organisations.

6. Request transparency regarding the workings and dependencies of commercial tools.

Industry partners play a key role in ensuring the utility and sustainability of an interconnected system of image and dose repositories. System integration, data consolidation, and overall workflow of a repository can be optimised by having, from the beginning of the project, full knowledge of the scope and workings of available tools, helped by the use of vendor-neutral terminology. Collaboration with and transparency from commercial vendors thus allows for the early detection of potential limitations that can be addressed and overcome during repository structure and coding scheme development. Such transparency is of particular importance when developing a system of linked repositories where the number of commercial tools is multiplied.

Therefore, it is recommended that the provision of clear documentation outlining the technical dependencies and required licensure associated with commercial equipment / tools be mandated by local, national, and international competent authorities, such as the European Commission Medical Devices Sector. Through these regulations, the effectiveness and long-term utility of imaging and dose repositories can be better ensured. Additionally, industry plays a central role in the implementation and wide-spread adoption of European / international standards and should develop technologies which integrate the use of harmonised terminology, quantities, units, etc., where available.

» Target audience: policy makers, regulatory authorities, industry.

7. Encourage the use of an application programming interface (API) in imaging and dose repositories and the continued development of proper meta-analysis tools to optimise data upload and analysis, respectively.

Incorporating an API in the repository structure enables larger volumes of data to be uploaded at one time, increasing efficiency of the system, and optimising clinical workflow. Additionally, meta-analysis tools and software packages that incorporate practical integrative tools and appropriate analysis techniques / models must continue to be developed to provide a more effective and user-friendly approach to conducting meta-analyses on large imaging and dose data sets. Comprehensive user guidelines should accompany all meta-analysis tools / software to ensure appropriate application and execution.

» Target audience: Euratom authorities, research communities, industry.

8. Encourage open-source repositories wherever manageable.

Repositories should be made publicly accessible wherever ethically and legally manageable, with special attention given to GDPR and associated legislation. This will, on one hand, facilitate the resources' wide-spread use, continued development, and increasing utility. It will also help ensure that clinical / research centres of all sizes have access to large, organised collections of high-quality image and dose data, thereby contributing to the advancement of radiation research. However, GDPR and the heterogeneous implementation of these regulations across EU member states puts constraints on open-source repositories.

A regulatory aspect requiring close consideration is the need for specific, informed, and unambiguous consent from an individual to use and store their personal data within the proposed system of repositories. Thus, efforts to enable open-source repositories should take into consideration the recommendations detailed in MEDIRAD Recommendation 1B section ('GDPR and Clinical Epidemiological Research') to help overcome these constraints. In the event open access is not feasible, intellectual property must be clearly defined and formally documented for all aspects of the repository, including future developments for the purposes of maintenance, use, and/or re-use.

» Target audience: health authorities, medical professional organisations, research community.

9. Encourage and support the interoperability of biobanks with image and dose data repositories, considering existing recommendations and infrastructure.

An interconnected system of image and dose data repositories should be compatible with other external repositories beyond the scope of medical imaging, nuclear medicine, and radiotherapy to maximise utility and impact. Biobanks (tissue and blood), for example, are an immensely valuable resource for advancing precision medicine and can play a major role in medical radiation and radiation protection research through a multisource integrative approach.

The biological samples housed within biobanks offer a wealth of information for clinical practice and for conducting robust clinical epidemiological, radiomic, and radiogenomic studies. To most effectively access and utilise available infrastructure in medical research, imaging and dose repositories and related biobanks should be developed with a goal of interoperability. To this end, it is recommended that EU / international organisations, as part of the forthcoming European Research Roadmaps from the EURATOM and HEALTH community, form dedicated working groups aimed at coordinating interoperability processes that are harmonised, collaborative and consider the infrastructures, outcomes and recommendations previously set forth by initiatives such as DoReMi, OPERRA, CONCERT, MELODI, BBMRI-ERIC, EURAMED, and most recently the European Health Data Space [6]. In this way, a robust network of harmonised health data can be implemented facilitating efficient information sharing and data consolidation.

» Target audience: research community, medical professional organisations.

1.3. MEDIRAD scientific achievements supporting recommendations

- Construction of an Image and Radiation Dose BioBank (IRDBB) across the 14 countries participating in the project, as proof of concept that an EU-wide repository for radiation research is feasible.
- Integration of different repositories in the IRDBB (DICOM and non-DICOM data).
- Optimisation of application programming interfaces (API) for uploading of and access to data from multiple clinical studies and geographic locations.

2

General Data Protection Regulation (GDPR) and Medical Radiation Protection Research.

Overall recommendation

1. **Harmonise GDPR implementation in medical radiation protection research.**
2. **Enhance the awareness regarding ongoing radiation protection research among public and patients.**

» **Specific recommendations:**

1. Set up a permanent group of experts at the European level.
2. Make extensive use of formal guidance documents that are reviewed and updated on a regular basis.
3. Promote the role of the data protection officer (DPO) among all institutions.
4. Organise and promote training courses on GDPR issues.
5. Ensure that the informed consent form about the use of personal data and biological samples is well written and clearly understandable.
6. Disseminate informative material about particular medical radiation protection research projects.

2.1. Justification

The MEDIRAD survey on problems encountered with the GDPR compliance process revealed that, for some MEDIRAD partners, the main difficulties were related to technical or procedural issues (related to the setting up of data protection measures but also procedural issues such as setting up training of personnel in GDPR), and with the lack of harmonisation of compliance rules among different countries or organisations.

Common guidance documents are intended to make the GDPR compliance process easier and more efficient. Their usefulness may be evaluated over time by periodically gauging the research community's opinion and making appropriate amendments and updates if needed. The survey also revealed that only one third of respondents used formal guidance documents (mainly national and in-house documents) for the management of GDPR protected data. A list of reference documents used by respondents is included in MEDIRAD RECO on GDPR Compliance Questionnaire Report (Annex 2).

The use of these documents was considered beneficial, underscoring the need to promote their use to streamline the compliance process. Support and advice from data protection officers (DPOs) from partner institutions, and other legal specialists, was also considered beneficial. Nonetheless, many researchers who completed the survey indicated poor knowledge of the existence of DPOs, indicating a lack of awareness and recognition of this profile. Researchers who completed the survey also expressed their willingness to improve their own knowledge and expertise in GDPR compliance issues.

Clinicians should also take into account that engaging with patients is not only a legal and ethical hurdle but is also a tool to raise patient awareness and trust in medical radiation protection research. The active involvement of the patients and, more generally, of the public in scientific research is nowadays considered of utmost importance both for the success of the research activity and for building the trust of the patients regarding the use of their personal data.

2.2. Implementation

1. Set up a permanent group of experts at the European level.

The group of experts on GDPR, composed by representatives of already existing national or local groups (e.g. those listed in Table 1 of Annex 2), belonging to research platforms in health related to Euratom research should guarantee a better and more efficient coordination between European countries, thus avoiding any divergence in the GDPR compliance process, through the drafting of guidance documents setting up common rules and procedures to implement, and comply, with the GDPR.

This group of experts should meet periodically with the scope of reviewing and updating common guidance documents (see next recommendation) and bringing together opinions and experience reported by the research communities from each country represented in the panel.

» Target audience: policy makers, regulatory authorities, research communities.

2. Make extensive use of formal guidance documents that are reviewed and updated on a regular basis.

The use of common guidance documents about GDPR compliance procedures can help harmonise the compliance process, and streamline the research activity of European projects, reducing setbacks and subsequent delays. Such documents should thus be consulted in the planning of medical radiation protection research projects in order to reduce differences in interpretation and practise. Some examples exist and can be found in Annex 2. These are intended to be living documents that are regularly updated by a group of experts (see previous recommendation) as well as a starting point for a fruitful dialogue between countries concerned.

» Target audience: medical professional organisations, research community.

3. Promote the role of the data protection officer (DPO) among all institutions.

Involve the DPOs of each partner institution from an early stage of the research project preparation and raise awareness among researchers about the existence and benefits of such experts. All institutional DPOs should be in contact with the DPO of the project itself in order to ensure that common procedures for GDPR compliance are followed by all partners.

» Target audience: medical professional organisations, research community.

4. Organise and promote training courses about GDPR issues.

Training courses should be organised at the national level, or within individual institutions, in order to brief researchers about GDPR issues when planning a research activity and/or setting up research infrastructures (database, biobanks, etc.). Courses should be delivered on national and international platforms in order to ensure the harmonisation of GDPR compliance mechanisms. They could also be required by law as normally happens for professional education and training. In particular, training of young people should be envisaged to guarantee correct education on GDPR issues from the beginning of their research careers.

» Target audience: research communities, industry.

5. Make sure that the informed consent form about the use of personal data and biological samples is well written and clearly understandable.

Increased awareness among patients about the scientific purpose of using their personal data will facilitate their decision to participate in a research project and to approve the use of their data for the project. Therefore, informed consent documents should be written in a comprehensible and accessible manner, with language that is accurate but not too technical. Clinicians should take time to carefully explain the objective and details of the specific research project, the need for patient data and biological samples, clarify any questions, and stress the procedures established to ensure security and the appropriate use of data and samples.

The ethical aspect linked to the use of personal data, samples, and images should also be explained i.e. that the research aims to benefit all patients in the future.

» Target: research communities.

6. Disseminate informative material about particular medical radiation protection projects.

As stated above, patients will be more willing to allow the use of their personal data if they understand the scope and purpose of the research project. Communication material such as flyers, social network content, infographics, and audiovisual material should be selected or prepared (if necessary) and shared with the public. Moreover, scientific outputs can be shared with the public through news stories and publications written in lay language. Engagement of patients and the public requires the allocation of budget specifically devoted to this activity in the research programme, and a case-by-case evaluation should be done to review the cost/benefit.

» Target audience: research communities, medical professional organisations, patient associations.

2.3. MEDIRAD scientific achievements supporting these recommendations

The main scientific achievements supporting the recommendations in Section 3 come from the MEDIRAD RECO on GDPR Compliance Questionnaire Report (see Annex 2 for detailed results). Overall, the survey reveals that researchers:

1. Are well aware about procedures to protect and manage patient's data.
2. Refer to EU, national and in-house documents for GDPR compliance.
3. Ask for harmonisation of compliance rules between different countries or organisations.
4. Lack knowledge of the role of the DPO in their institution and in the framework of the project.
5. Ask for training courses with common shared programmes on GDPR compliance.

3

Annex 1
Supporting evidence resulting from MEDIRAD research.

MEDIRAD Scientific Goals and Research Results

Coding and Structured Reporting.

Radiology departments use varying descriptions for imaging procedures (study names) with many national systems mainly used for billing. This variation limits the practicality of utilising the data produced from these procedures for research and quality assurance and presents a major barrier to establishing image and dose registries. To help overcome this variability in reporting, International standards and profiles are available for such processes, for example DICOM Structured Reporting objects or IHE MRRT-Profile (Management Radiology Reporting Templates). Different coding sets are also available, which include but are not limited to SNOMED CT for general coding in medicine or RadLex (by RSNA) for specific items in radiology.

Standards in coding and reporting offer several benefits, including:

- Structured data capture to ensure better quality and completeness of reports
- Validation while reporting
- Easier visualisation of pathological findings (e.g. display in another colour)
- The ability to combine medical findings and dose reports (DICOM RDSR)
- Coding schemes that enable categorisation of findings and comparison between different sites
- Structured reporting enabling pooling of reports (e.g. for research or epidemiological work-up)

As part of MEDIRAD, several catalogues for coding clinical studies in the MEDIRAD context have been developed based on RadLex [9]. For reporting, a standards-based reporting tool (MRRE) has been developed. This is based on the IHE MRRT profile to support coding, exchange of templates, and aggregation of results.

As an additional feature, a natural language processor (NLP) based check for consistency of the reports is included that allows for the comparison of requests from the clinical information with the findings and impression components of the reports. Additionally, dose reports for imaging studies (DICOM RDSR) can be combined with the reporting of the content itself, thus fulfilling European legal requirements. Additionally, the visualisation of findings can be improved, for example by highlighting pathological findings to be displayed in different colours. The reporting tool is fully integrated with the KHEOPS platform, which is used for the management of imaging studies in MEDIRAD.

Imaging and Dose Repositories.

A European level imaging and dose data repository, named the Image and Radiation Dose Biobank (IRDBB), was developed to enable the collection, storage, and retrieval of de-identified image and dose data relevant to the MEDIRAD project [10]. The IRDBB comprises three integrated components:

1. DICOM repository, that receives and stores the DICOM data (images and dose data) and provides query/retrieval to the end-users based on pre-existing open-source PACS software including structured reports (DICOM SR) and other DICOM-compliant data structures, such as exchange of dose data and technical parameters of the examination. The DICOM repository is capable of managing all imaging modalities considered in MEDIRAD.

2. DICOM import software, that interacts with data on the client's side, enables a zero footprint (no software installation on the client side), selects data to be sent to the central repository, ensures de-identification, on-the-fly lossless compression, and sends data to the central DICOM repository, with management of large volume transfer. Data transmission uses DICOM web services that facilitate communication over the web and across the firewalls of healthcare enterprises.

3. Semantic repository (referred to as RDF) for non-DICOM dose data. Unique identifier sets link the DICOM and RDF repositories. An application ontology has been created, covering the information domain specified by experts. Software has also been developed to populate the RDF repository, both from DICOM metadata and from data expressed in other ad-hoc formats.

The MEDIRAD project, under the guise of the IRDBB, as detailed above, has provided proof-of-concept for a regional patient dose and imaging registry within Europe. Following on from this initiative, the MEDIRAD consortium supports further research, development and wide-spread adoption of image and dose repositories for the purposes of optimising radiation protection research and patient care. Full reports on repository setup, piloting and catalogue development in the context of MEDIRAD can be accessed via the MEDIRAD website.

MEDIRAD RECO on GDPR Compliance Questionnaire Report

Drafted by **S. Della Monaca**, **V. Dini**, **S. Grande** e **A. Palma**, WP6

The online survey on GDPR Compliance developed by WP6 was launched on 01/02/2021 and closed on 28/02/2021.

We collected 37 answers from researchers, members of 21 different institutions and involved in WP 2-6 of the MEDIRAD Project (Questions 1-4, Figure 1).

Figure 1
Wich MEDIRAD Work Package(s) are you involved in?

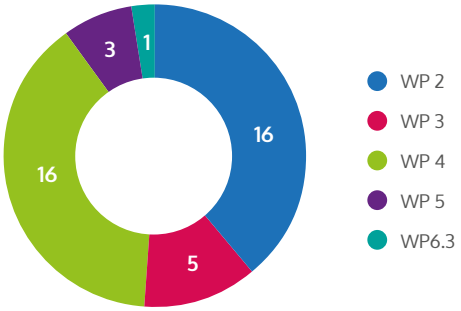
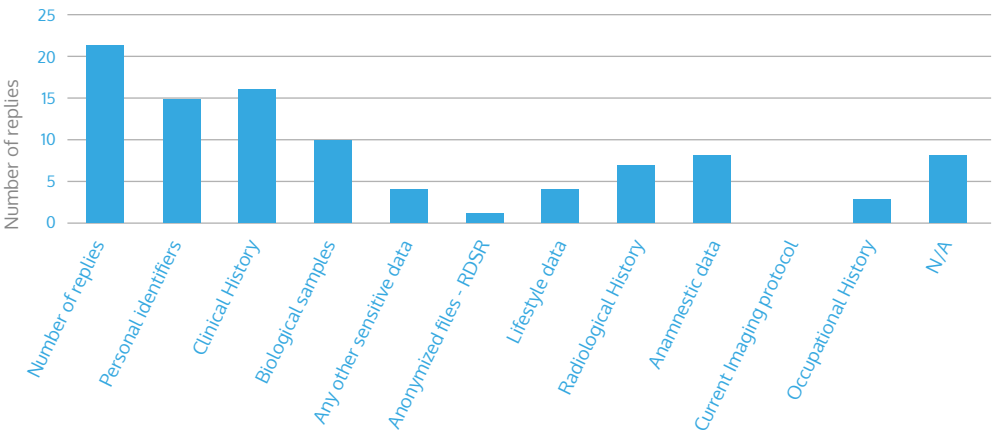


Figure 2
Type of nominative patient data collected

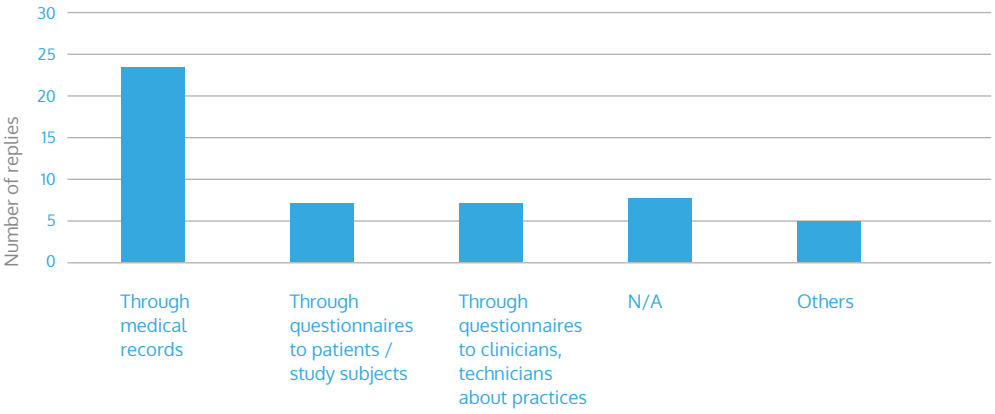


In Figure 2 the distribution of answers to question 5 are shown, i.e., how many respondents declared to collect each type of nominative patient data. Multiple answers were allowed. It comes out that the three most frequent type of data collected are Any type of clinical images (21/37 declared to collect them), Personal identifiers (15/37) and the Clinical history (16/37).

From question 6 (If you answer "Any other sensitive data" in the previous question, please specify) it comes out that Any other sensitive data are dosimetric data (two answers) or vital status data and cancer incidence data (one answer).

Figure 3 describes the distribution of answers to question 7 (How were these data obtained?) and it comes out that the most employed method to collect data is the Clinical registry (24/37). Other listed method (Questionnaires to patient/study subject and Questionnaires to clinicians, technicians about practices) were equally distributed and much less frequent (6/37 both). A few respondents (5) added other options, such as PACS, linkages with disease registries, through the International Regulatory Database (IRDB). Exactly the same respondents who answered N/A to question 5, coherently answered N/A to this question.

Figure 3
How were these data obtained?



Question 8 concerns what procedures have been set up for protecting MEDIRAD patient related data during storage, management, exchange, and processing. The question allowed multiple answers.

Figure 4 shows that 28/37 people have taken data protective measures, 25/37 relied on ethics approvals, 19/37 on informed consent and the 15/37 stated that patients have been informed of their right of access to their personal medical information stored in relation to the MEDIRAD project. The histogram suggests that several measures have been taken at the same time to ensure data protection.

Figure 4

What procedures have you set up for protecting MEDIRAD patient related data through storage, management, exchange and processing?

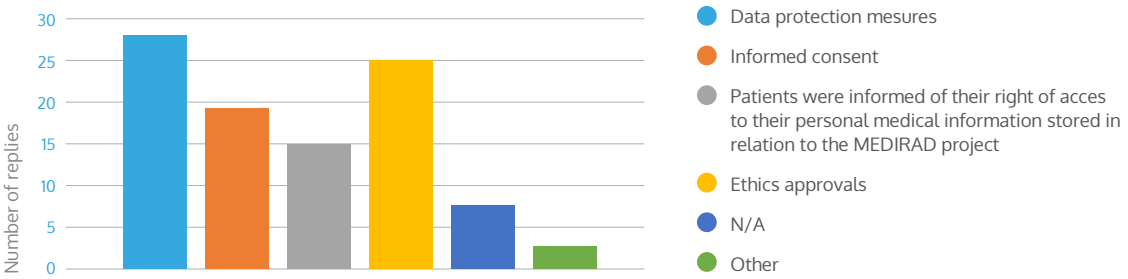
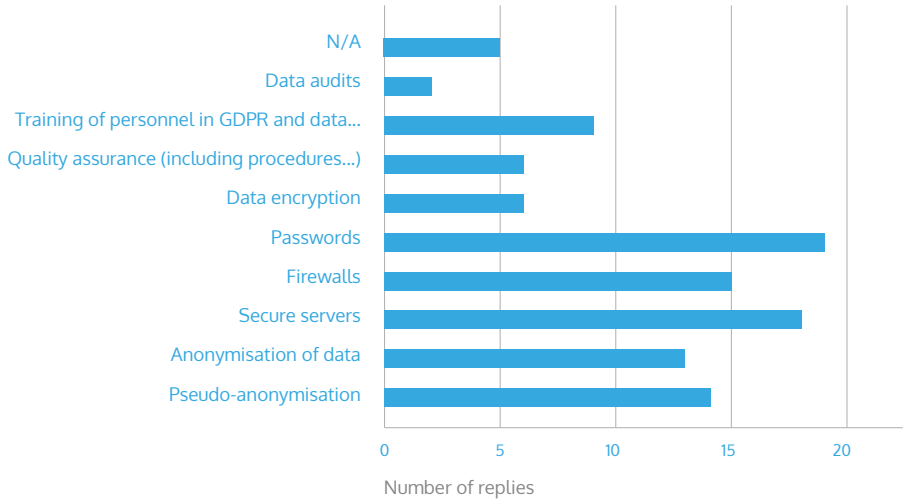


Figure 5

If you answer "Data protection measures" in the previous question, please specify.



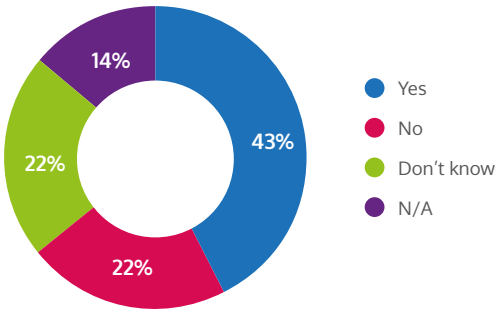
With regard to the Data protection measures, the main measures taken were password (19/37 people), secure servers (18/37 people), firewalls (15/37 people), pseudonymisation (14/37 people), and anonymisation of the data (13/37 people) (Figure 5). The other measures were adopted in lower numbers (from 2 to 9), and, in particular, the last one was audits (2/37 people).
Regarding the question 10 about Data protection procedures/measures we received only the following three comments:

- Seems that every clinical centre has its own understanding of the procedures to implement to comply with GDPR.
- The patient records arrive already anonymised to me.
- Patient anonymisation and imagine anonymisation sent to unique server.

Question 11 investigated whether a DPO had been appointed within the respondents's organisation as part of the MEDIRAD project (Figure 6). 43% of the answers are affirmative while the remaining 47% is distributed between No (22%), I don't know (22%), and Not Applicable (14%).

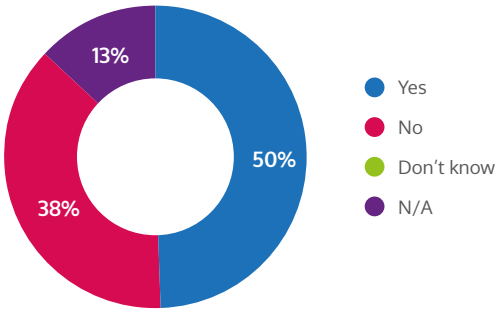
This data is quite significant, possibly indicating a lack of adequate information about GDPR compliance issues together with a lack of clarity in the way of the question was formulated. Possibly, to avoid ambiguity and maybe get less "I don't know" answers, a more suitable way of writing the question would be: Was the DPO operating in your organisation involved in your MEDIRAD research activity?

Figure 6
Are there nominated "data Protection Officers" (DPOs, as defined by GDPR) within your organisation in the context of MEDIRAD research?



People who answered Yes to Question 11 were then redirected to Question 12, in which they were asked if they had received support from their DPO. The percentages are shown in Figure 7. Again, a lack of clarity of the previous answer is evident also in this graph. Some of the respondents who declared to have involved their own organisation's DPO in the MEDIRAD activity stated that the issue of whether a support/advice was in fact provided is 'Not Applicable', which is quite unlikely.

Figure 7
If you answered "Yes" to the previous question, have you received support/advice from these DPOs?



Almost one third (32%,12/37) of the respondents affirmed to refer to formal guidance documents for the management of GDPR protected data in the framework of MEDIRAD project (Question 13, Figure 8). The nature of such guidance it is equally distributed between national and in-house documents; one respondent referred to EU documents (Figure 9, Question 14: this question allowed multiple responses).

Figure 8
Did you refer to formal guidance documents for the management of GDPR protected data in the MEDIRAD project?

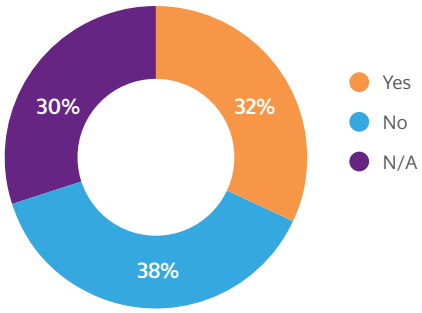
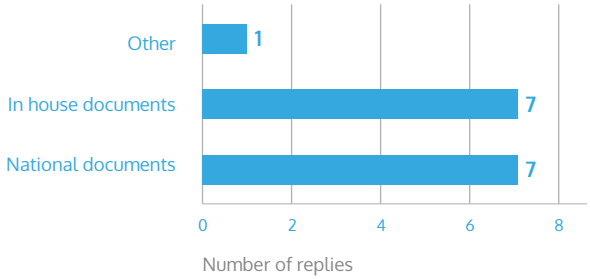


Figure 9
If you answered "Yes" to the previous question (13), pplease specify the nature of such guidance.



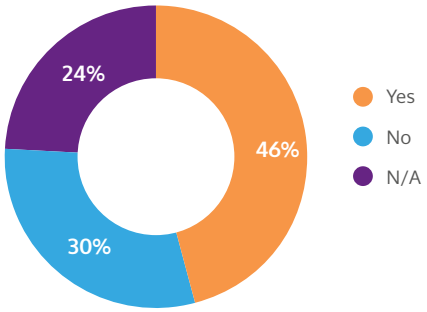
In addition to the use of GDPR, some in-house or national documents were cited by respondents. The references of such documents (Question 15) are reported in Table 1, together with the institution and the State of the corresponding respondent.

Table 1
ANSWER TO QUESTION N.15

Guidance documents	Institution	State
Wet Persoonsregistratie (WPR) Wet Geneeskundige Behandeloverenkomst (WGBO) Privacy Kader UMCG	University Medical Center Groningen	The Netherlands
In house GDPR guidance The Data Protection Act 2018	The Royal Marsden National Health Service Trust	UK
https://www.upc.edu/normatives/ca/proteccio-de-dades/normativa-europea-de-proteccio-de-dades/drets	Universitat Politécnica de Catalunya	Spain
Via ethical committee	Universiteit Gent	Belgium
Documents from the CNIL (Commission Nationale de l'Informatique et des Libertés)	Institut de Radioprotection et de Sûreté Nucléaire	France

Moreover, almost a half of the respondents declared to have benefit from oral guidance form their own organisation's DPO or other legal specialists (Question 16, Figure 10).

Figure 10
Did you also benefit from oral guidance from your organisation's DPO or other legal specialists?



No major impacts (some delays or even no notable impact) to ensure GDPR compliance in MEDIRAD activities have been reported by the majority of the respondents; however, the development of alternative solutions in order to ensure compliance or, even, the impossibility of carrying out a part of the research were declared by a minority of MEDIRAD researchers. (Figure 11, Question 17: this question allowed multiple responses).

Figure 11
What was the impact of GDPR compliance issues on your work in MEDIRAD?

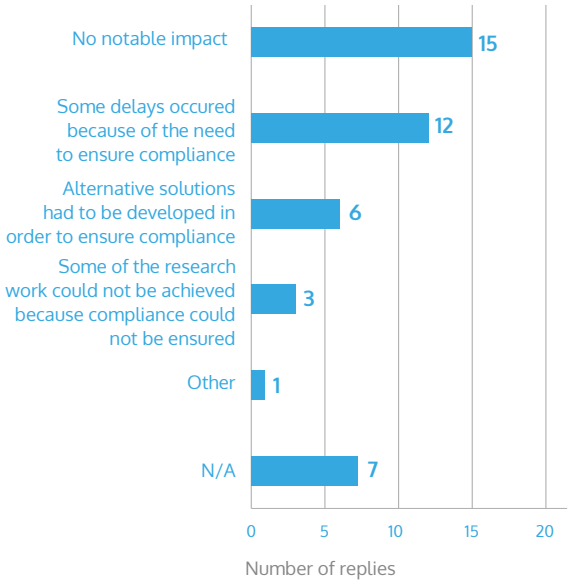
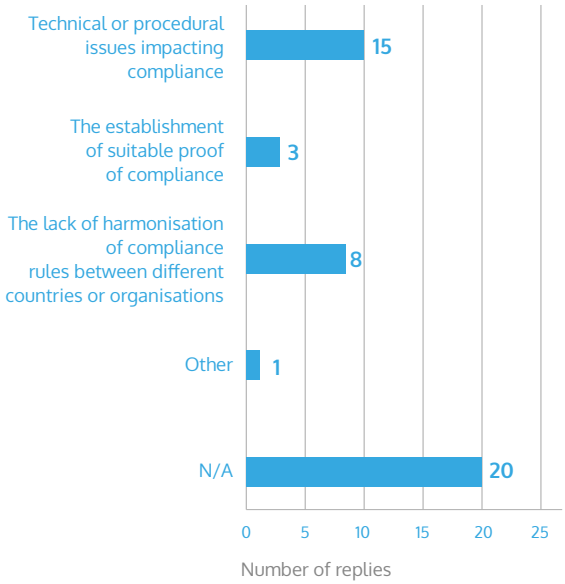


Figure 12
If difficulties with GDPR compliance occured, were these mainly related to:



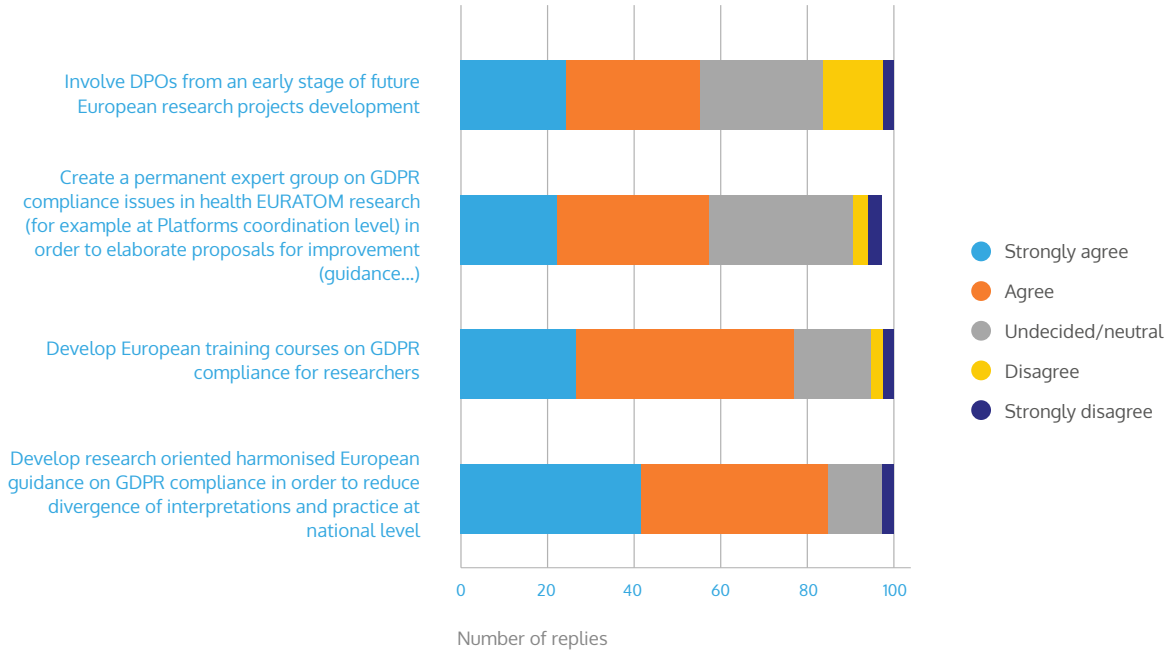
The difficulties with GDPR are mainly correlated with technical or procedural issues and with the lack of harmonisation of compliance rules among different countries or organisations. Most respondents, however, stated that they did not encounter any difficulties (Figure 11, Question 18: this question allowed multiple responses).

One researcher declared that patients who declined permission to get access to their medical file were withdrawn from the study. Moreover, another researcher declared that local partners (such as a local health agency) claim that they have no right to use the address to contact patients (cases and controls) (Question 19).

In the following, responses to the Questions 20-23 On the basis of your experience within the MEDIRAD project, please rank your agreement about the following suggestions for facilitating GDPR compliance in future health related European research projects (Ranking: 1. Strongly disagree; 2. Disagree; 3. Undecided/Neutral; 4. Agree; 5. Strongly agree) will be shown (Figure 13). Erroneously, Question 22 was set as non-mandatory, and one responder did not provide any answer, so answers were received from 97.3% (i.e. 36/37) of the total sample.

From Figure 13 it is evident that the two most rated recommendations, with a sum of agree and strongly agree of about 80% of the total respondents, are Develop research oriented harmonised European guidance on GDPR compliance in order to reduce divergence of interpretations and practice at national level, with the highest percentage of strongly agree (43%; 16/37) and Develop European training courses on GDPR compliance for researchers. It is worth noticing that only one respondent answers strongly disagree for each listed option and that this respondent was the same for all topics.

Figure 13



The remaining two options, Create a permanent expert group on GDPR compliance issues in health related EURATOM research (for example at Platforms coordination level) in order to elaborate proposals for improvement and Involve DPOs from an early stage of future European research projects development also got more than 50% of positive feedbacks (i.e. sum of agree and strongly agree) but received a higher number of undecided/neutral (35%, 13/37 and 29%, 11/37, respectively).

From the analysis of questions 20-23 it comes out that researchers are generally more favourable in improving their own knowledge and expertise in GDPR compliance issues than receiving support or advice from DPOs and expert groups, though the difference in approval of the listed options, translated in absolute numbers appear to be non-significant (30 respondents for the two best rated options versus 19 for the two least rated).

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MEDIRAD

RECOMMENDATION 2

OPTIMISATION OF IONISING RADIATION-BASED MEDICAL PROTOCOLS FOR DIAGNOSTICS OR THERAPY

PROJECT TITLE

Implications of Medical Low Dose Radiation Exposure

This project has received funding from the Euratom research and training programme 2014–2018 under grant agreement No 755523.

Introduction

MEDIRAD has conducted research on five key elements for further optimisation of radiation-based medical protocols for diagnostics or therapy. The related results have led to the elaboration of novel practical recommendations in the following fields.

1. Optimisation of image quality and dose in CT scanning, including CT in multimodality imaging and paediatric CT scanning

Computed Tomography (CT) is the largest contributor to the European population's collective exposure from medical uses of ionising radiation, and poses a potential health risk to patients [1, 2]. It is thus critical to employ the principle of optimisation in radiological protection to ensure doses are as low as reasonably achievable (ACLARA), unproductive exposure is avoided, and the benefit to risk ratio is maximised for all CT examinations [3]. This is of particular importance for the paediatric population as a result of their higher radiosensitivity and prolonged life expectancy [3]. While dose reduction inherently reduces the risk of potential harmful radiation effects, the extent to which doses can be reduced is constrained by image quality, which in turn is dependent on clinical needs [3-5]. Therefore, to effectively optimise exposure to ionising radiation from CT examinations and multimodality imaging, optimisation strategies should be based upon patient and organ dosimetry, image quality, patient characteristics, and clinical indications. The development of robust optimisation tools that account for each of these contributing factors, along with further advancements in personalised medicine, are therefore needed.

2. Patient-specific dosimetry in molecular radiotherapy (nuclear medicine therapy)

Patient-specific dosimetry to assess the radiation absorbed doses in target volumes and organs at risk is important to understand and improve the safety and efficacy of both existing and new radiopharmaceuticals. The planning and confirmation of absorbed doses is required under Council Directive 2013/59/Euratom [6] for molecular radiotherapy (MRT) as well as for external beam radiotherapy (EBRT). The evaluation of patient dosimetry on an individual basis can help to highlight the range of absorbed doses delivered from empirically-based fixed administrations of activity and the consequent range of likely outcomes, including long-term risks of secondary malignancies.

Multi-centre studies are required to develop personalised treatments with radiotherapeutics due to the limited numbers of patients treated at single centres. Individualised biokinetics should be considered rather than models and values established for a healthy population, and biomarkers of radiosensitivity can inform further levels of personalisation. While the clinical studies performed within MEDIRAD focused on radioiodine therapy for thyroid cancer, the methodologies developed for harmonised data collection and analysis are widely applicable to existing, and novel, radiotherapeutics as MRT experiences rapid expansion.

3. Breast radiotherapy and secondary cardiovascular risks: establishing risk models for clinical support and improving individual risk assessment with the help of specific biomarkers

Breast cancer (BC) is among the most commonly diagnosed cancers in women. Around 21% of BC cases occur in women younger than 50-64 years of age and 35% occur in those aged 50-64. Radiotherapy plays a pivotal role in the treatment of breast cancer BC patients, but may induce cardiac damage and subsequent major cardiac events like acute coronary events, which may occur relatively early or up to decades after completion of radiation treatment. As overall survival of BC patients has significantly improved, the prevalence of BC survivors at risk of developing cardiac toxicity is increasing. This is relevant at the individual level, as cardiac toxicity has a major impact on quality of life and leads to increased morbidity and mortality, but also at the societal level, as it leads to secondary health costs and may interfere with daily functioning and subsequent labour participation.
Therefore, identification of BC patients at high risk for cardiac toxicity is crucial for developing effective strategies for individualised primary and/or secondary prevention of cardiac toxicity.

4. Breast cancer radiotherapy: practical aspects on heart sparing

The radiation dose to the heart is an important risk factor for radiation-induced cardiac toxicity and it has been generally acknowledged that there is no threshold dose below which no toxicity will occur. Therefore, cardiac dose should be kept as low as reasonably achievable (ALARA) to prevent radiation-induced cardiac events.

There are several options to lower the dose to the heart, e.g. by means of reducing the radiation target volume (e.g. partial breast irradiation) and/or using more advanced radiation techniques (e.g. breath hold techniques and proton therapy). However, not all patients are suitable candidates for reducing the target volume. In addition, applying more advanced radiation techniques generally requires more resources, is more expensive, and may be more burdensome to patients.

Although there is an increasing awareness among radiation oncologists that sparing the heart is essential to broaden the therapeutic ratio in BC patients, the currently available options are not always applied in routine clinical practice.

5. Modelling of patient dosimetry at the voxel scale

Patient dosimetry is an essential part of ensuring quality and safety both in radiotherapy and diagnostic imaging. In radiotherapy, the determination of the radiation doses has to be improved, especially in nuclear medicine therapy. In external radiotherapy, knowledge about radiation dose, especially outside the planning target volume, also has to be improved. It is therefore necessary to move from planned dose distribution to delivered dose distribution in order to improve the quality of care, including person-centred care, and the radiological protection of the patient. In diagnostic imaging, where the radiation dose is not planned for individual patients, better knowledge about the radiation dose to organs is needed to improve optimisation in general and for individualisation of imaging processes.

Today, to a great extent, only radiation dose indices are used to document patient doses. This lack of information hinders real optimisation and can also conceal radiation-related risks to specific organs also in the field of diagnostic imaging.

Recent advances in computer science will facilitate progress in this field, since the specific constitution of the patient, as well as technical parameters specifying the exposure, are now available and usable for dose estimation. Internal dosimetry can also include information from molecular imaging to advance the knowledge about patient-specific biokinetic data. The MEDIRAD project has made several contributions to this end.

The following science-based policy recommendations have been produced in an effort to advocate and facilitate the further development of tools and techniques to optimise both image quality and patient exposures to ionising radiation. They are addressed to different stakeholders in an effort to disseminate and implement the project's key findings and learnings.

1

Optimisation of image quality and dose in CT scanning, including CT in multimodality imaging and paediatric CT scanning.

Overall recommendation

Develop and implement robust tools for optimisation of CT scanning and multimodality imaging that account for whole-body and organ-specific dosimetry, image quality, and radiogenic risk.

» **Specific recommendations:**

1. Accompany all exposure documentation and reporting by suitable measurable indicators of image quality.
2. Evaluate organ doses prospectively and retrospectively in patient sub-cohorts to assess individual risks and better inform patient management.
3. Pay special attention to keep doses to radiosensitive organs to a minimum while maintaining appropriate image quality, especially in paediatric populations undergoing recurrent CT exams.
4. Encourage further research into methods to accurately estimate individual patient organ doses.
5. Support the transfer of image quality assessment tools developed in MEDIRAD to other clinical indications, both for chest CT and other CT protocols.
6. Support further research and development towards an integrated dosimetry and image quality approach that incorporates equipment-specific, patient-specific, and protocol-specific assessments of exposure.
7. Establish indication-specific diagnostic reference levels (DRLs) for organ dose values that are accompanied by image quality reference levels (IQRLs).
8. Encourage standardisation of CT radiation exposure in nuclear medicine to improve optimisation of multimodality imaging.

1.1. Justification

CT scanning is being increasingly used for diagnosis based on imaging and contributes considerably to radiation exposure among the population. Therefore, optimisation in terms of benefit-to-risk ratio is of extreme importance, particularly for paediatric applications. On the basis of experience acquired through the MEDIRAD project (see Annex 1), this recommendation aims to overcome current barriers to achieving effective and efficient optimisation in CT scanning and multimodality imaging by translating the MEDIRAD research findings into daily clinical routine procedures. Additionally, it encourages the extension of MEDIRAD's overarching methodological approach beyond CT scanning and multimodality imaging, in order to develop an integrated optimisation system for diagnostic radiology, interventional radiology and nuclear medicine imaging.

1.2. Implementation

1. Accompany all exposure documentation and reporting by suitable, measurables, indicators of image quality.

Optimisation of the benefit-to-risk ratio for imaging procedures can only be achieved if the exposure is reduced in a way that guarantees appropriate image quality, maintaining diagnostic accuracy for the pathology/clinical indication of interest. Therefore, in all future optimisation studies, both the exposure, preferably as organ doses, and the image quality derived from the corresponding patient images (e.g. by way of the MEDIRAD project's semi-automatic evaluation of physics-based image quality parameters [5]) have to be determined.

If broadly established, fast and objective image quality and dose evaluations could greatly benefit the diagnostic use of ionising radiation and facilitate easy approaches to quality assurance. It is important that this approach is easy to implement and does not increase the workload of the clinicians. A most promising approach would be to integrate such tools in the vendors' software, and appropriate steps should be taken in this direction.

» Target audience: practitioners, policy makers, regulatory authorities, medical professional organisations, research community.

2. Evaluate organ doses prospectively and retrospectively in patient sub-cohorts to assess individual risks and better inform patient management.

Patient organ doses from thoracic CT may rise to tens of mGys and even exceed established thresholds for tissue effects after repeated CT acquisitions. These doses, and the potential resulting risk of radiation induced malignancies or other health effects, should not be ignored. Practitioners (including radiologists, cardiologists, oncologists, radiographers), in collaboration with the research community, should make a concerted effort to record organ doses and follow

various sub-cohorts of patients over time (i.e. years to decades) as a means of monitoring primary exposure and evaluating individual risk. MEDIRAD has developed methods to estimate patient organ dose for chest CT examinations and determine image quality, integrating state-of-the-art objective and subjective image analysis [5,7]. It is recommended that practitioners / investigators implement these methods alongside established risk calculations as robust optimisation tools in thoracic CT scanning. Additionally, the MEDIRAD method of organ dose estimation can be employed retrospectively as a means of informing current patient management. It also offers a tool to expedite epidemiological research related to dose effects and radiation induced risk for the selected thorax protocols.

» Target audience: practitioners, research community, regulatory authorities, patient associations.

3. Pay special attention to keep doses to radiosensitive organs to a minimum while maintaining appropriate image quality, especially in paediatric populations undergoing recurrent CT exams.

The risk of stochastic radiation effects in the paediatric population has been shown to be at least twofold higher than in adult patients. Additionally, severely ill (in particular neurologic and haematologic) paediatric patients may undergo multiple CT studies of the head and thorax in a short period of time. A significant percentage of active bone marrow is present in the cranium, ribs, and vertebrae of young children, and effective dose estimation does not adequately describe dose variations in superficially located organs.

Therefore, novel methodologies must be employed to better estimate and further optimise CT examinations within the paediatric population as a means of keeping organ-doses as low as reasonably achievable while still maintaining appropriate image quality. The MEDIRAD project provides new evidence to inform dose reduction strategies that focus on tube current modulation and tube voltage selection techniques [8,9]. Practitioners, medical professional organisations, and the research community are encouraged to incorporate and further develop these findings into robust and practicable organ-dose reduction methods that can be widely implemented within the clinical setting.

» Target audience: practitioners, medical professional organisations, research community, regulatory authorities, patient associations.

4. Encourage further research into methods to accurately estimate individual patient organ doses.

Further research efforts should be employed to estimate doses to partially irradiated organs such as the thyroid and liver. This is particularly important for patients undergoing multiple CT scans, given the heightened risk associated with cumulative organ-doses. Over-ranging can represent a significant portion of the overall exam dose, particularly for short scan lengths. A patient-specific method for the estimation of organ doses based on Monte Carlo calculations will be useful for CT optimisation and as input for epidemiological research and modelling of radiation induced risks.

It is expected that this could have an important impact on reducing doses to partially irradiated organs. Medical professional organisations and the research community are encouraged to direct future research efforts on using the capabilities of modern CT scanners employing beam overscanning, organ-based tube current modulation, as well as on indication-specific scan protocols in order to optimise the scan length, beam collimation, pitch, and effective mAs.

» Target audience: practitioners, research community, regulatory authorities, research community, patient associations.

5. Support the transfer of image quality assessment tools developed in MEDIRAD to other clinical indications, both for chest CT and other CT protocols.

Within the scope of the MEDIRAD project, an approach for semi-automatic evaluation of physics-based image quality parameters [5], which is correlated with subjective image quality evaluations, has been developed for three clinical indications for Chest CT: mycobacterial infections and pulmonary tuberculosis; interstitial pathology (suspicion of pulmonary fibrosis); and pulmonary metastases and nodules.

Given the positive MEDIRAD findings, practitioners and the medical research community are encouraged to translate the current evaluation technique to other relevant clinical indications (e.g. aortic disease), as well as CT protocols beyond the thoracic region (e.g. head and neck, abdominal/pelvic). When prioritising allocation of research efforts, clinical needs and feasibility of clinical implementation for the specified indication must be taken into account to ensure maximum impact of research outputs.

» Target audience: practitioners, research community, regulatory authorities, research community, patient associations.

6. Support further research and development towards an integrated dosimetry and image quality approach that incorporates equipment-specific, patient-specific, and protocol-specific assessments of exposure.

To best optimise CT scanning it is important to consider the diagnostic quality of the image based on clinical needs, the radiation dose to the patient, which should be as low as reasonably achievable, and the examination exposure techniques based on relevant protocols. To this end, CT dosimetry should be patient-specific, equipment-specific, and protocol-specific. There are currently no systems that offer a fully integrated approach; however, the MEDIRAD project's methodology and associated tool for determining image quality and patient organ dose offers a valuable path forward (see Annex 1 for detailed information).

On this basis, further research and development should be encouraged to realise a robust and fully integrated system for CT dosimetry and diagnostic image quality that allows for traceability of all generated data and is applicable to CT imaging of any region of the body.

» Target audience: practitioners, regulatory authorities, medical professional organizations, research community, industry.

7. Establish indication-specific diagnostic reference levels (DRLs) for organ dose values that are accompanied by image quality reference levels (IQRLs).

The current approach to establishing diagnostic reference levels (DRLs), as outlined in ICRP Publication 135 [10] and mandated under Council Directive 2013/59/EURATOM [6], is an effective method for optimising medical exposure to ionising radiation; however, CT exposure could be further optimised through the incorporation of indication-based organ dose values and accompanying image quality reference levels (IQRLs). Policy makers and the radiation protection research community are encouraged to further explore the establishment of organ dose values with accompanying IQRLs as a more nuanced approach to DRL-based optimisation. This novel approach should have regard for clinical needs, prioritising the most prominent examinations with notably high doses of radiation for maximum impact.

Clearly, there are many steps to be taken in terms of development to allow fully automated evaluations to be stored in databases relevant for DRL applications. In addition, it is necessary to educate and train the medical professionals as well as regulators regarding organ dose-based DRLs and IQRLs. These new approaches, while slightly more complex than the existing DRLS, allow for more efficient optimisation. The system for evaluations of organ dose values and image quality parameters must be fully automated to avoid new barriers for adopting the DRL concept. It is important to foster the DRL concept in general and provide support to the different countries within the EU need in adopting this concept.

» Target audience: policy makers, regulatory authorities, research community.

8. Encourage standardisation of CT radiation exposure in nuclear medicine to improve optimisation of multimodality imaging.

The establishment of European DRLs for specific applications of CT in multimodality imaging has proven extremely difficult, notably because numerous CT dose indicators are currently in use across Europe [11]. A standardised approach to calculating and reporting CT radiation exposure is required to significantly improve optimisation of multimodality imaging and allow a better standardisation of CT applications in nuclear medicine. A holistic optimisation approach should be taken, accounting for both the CT and nuclear medicine components.

DRL quantities of CTDIvol and DLP should be used for CT radiation exposure, while effective dose or even organ doses are recommended as a means of comparing the effects of CT and nuclear medicine procedures. The effective doses and organ doses can be used as a potential benchmark quantity for combined irradiation in hybrid imaging. Again, standardisation of protocols for CT applications in hybrid imaging is essential. Suitable databases are also required to compare procedures from various hospitals throughout Europe and optimise these procedures in a harmonised way.

» Target audience: policy makers, regulatory authorities, medical professional organisations, research community.

1.3. MEDIRAD scientific achievements supporting recommendations

- Dose evaluation tools, in tandem with correlated objective and subjective image quality evaluations of chest CT examinations, have been integrated into a freeware, open access, modular software expert system, which can be used to determine patient-specific exposure descriptors as well as patient-specific image quality parameters and thus identify the optimal Chest CT protocol.

- MEDIRAD has studied how to improve the direct estimation of cancer risk following low doses of ionising radiation from CT scanning in childhood and adolescence and has investigated factors, such as genetic and epigenetic variants, which may modify this risk. More information is found in Annex 1.

2

Patient-specific dosimetry in molecular radiotherapy (nuclear medicine therapy).

Overall recommendation

Develop and implement dosimetry-based protocols for molecular radiotherapy across Europe.

» **Specific recommendations:**

1. Develop a roadmap for dosimetry-based treatment planning and verification of the radiation doses delivered to target volumes and organs at risk for treatments with radiotherapeutics.
2. Provide adequate resources, including medical physics support to perform patient dosimetry, to centres providing radionuclide therapy.
3. Support development of observational and interventional multi-centre, multi-national clinical studies.
4. Harmonise the implementation of Council Directive 2013/59/Euratom with respect to patient dosimetry within Europe.
5. Record radiation doses and treatment details in dose data repositories..

2.1. Justification

The radiation doses delivered to patients undergoing molecular radiotherapy (MRT) can be calculated from quantitative imaging of the biodistribution of uptake of a radiotherapeutic, a capability unique to nuclear medicine. Patient-specific dosimetry may be used to personalise treatment planning and to verify the radiation doses delivered, as mandated by Council Directive 2013/59/EURATOM [6].

The need to improve clinical and cost effectiveness of existing and new radioactive drugs, and to evaluate the risks entailed by their use, are of increasing importance as the field undergoes rapid expansion. Multi-centre clinical studies are necessary to overcome the limited number of patients treated in individual centres. Within MEDIRAD, the radiation doses delivered to patients undergoing radioiodine treatment for low and intermediate risk thyroid cancer were calculated in four centres, in three countries, through a multidisciplinary approach involving medical physics, nuclear medicine, and radiation oncology.

Site visits were performed to prepare imaging systems for quantitative imaging and dosimetry was performed centrally in two centres. The studies demonstrated the feasibility of acquiring, processing, and collating dosimetry data. In addition, pharmacokinetic modelling was performed and a protocol for a prospective epidemiological study was developed to assess the risks of low dose radiation. A further study of radiosensitivity biomarkers is reported separately.

2.2. Implementation

1. Develop a roadmap for dosimetry-based treatment planning and verification of the radiation doses delivered to target volumes and organs at risk for treatments with radiotherapeutics.

Currently, the majority of MRT procedures are performed using empirically-based fixed activity administrations of radioisotopes. This leads to a wide range of absorbed doses delivered both to tumours and to organs at risk, as also shown by results from MEDIRAD. While quantitative imaging and dosimetry is feasible for therapy procedures, possibly aided by 'companion diagnostics', dosimetry is not routinely performed [12, 13].

However, patient-specific dosimetry is mandated and recommended by Council Directive 2013/59/Euratom [6], ICRP Publication 140 [17] and position statements from medical professional organisations [19-21], and has been incorporated into national legislation.
A coordinated European approach should be developed in consultation with all relevant stakeholders, including nuclear medicine and radiation oncology, to enable dosimetry-based treatment planning and verification of the radiation doses delivered, with initial focus on therapeutic procedures of greatest clinical and cost impact.

» Target audience: policy makers, regulatory authorities, medical professional organisations, research community.

2. Provide adequate resources, including medical physics support to perform patient dosimetry, to centres providing radionuclide therapy.

Many centres currently do not have sufficient medical physics support or the necessary resources to prepare scintillation cameras and ancillary equipment for quantitative imaging or to perform routine calculation of absorbed doses in MRT.

Existing training schemes should guarantee a constant supply of suitably qualified medical physicists with a comparable level of training, to enable local data processing supported by external validation and quality control. MEDIRAD has demonstrated that dosimetry verification of radioiodine therapy is feasible but that an infrastructure is necessary to acquire, process and analyse the data and to report the results. The healthcare costs of setting up the necessary infrastructure should be supported alongside the cost implications of new radiotherapeutics.

» Target audience: policy makers, regulatory authorities, medical professional organisations, research community.

3. Support development of observational and interventional multi-centre, multi-national clinical studies.

Currently, clinical trials of novel radiotherapeutics incorporate a limited degree of dosimetry, with little or no consideration of dosimetry-based treatment planning. It is therefore of particular importance that patient-specific dosimetry is fully integrated into early and late phase clinical trials, and that results are made available to clinical users. This will require close collaboration between industry, professional societies and academic research.

MEDIRAD has shown the practical feasibility of multi-centre clinical studies incorporating patient dosimetry, although there is a need to conduct these as single multi-national studies under the umbrella of international organisations such as the EORTC, rather than as separate studies as was done in this project. Protocols developed within MEDIRAD for site set-up measurements and for dosimetry calculations should be further refined in collaboration with national and international societies. To support under-resourced centres, MEDIRAD performed site visits for the preparation of imaging systems and centralised dosimetry calculations in 'dosimetry hubs', an approach that should be further explored (see Annex 1 for details).

In addition, interventional trials are required to investigate the clinical and cost effectiveness of personalised dosimetry-based treatments with radiotherapeutics. To facilitate multi-national trials, regulatory authorities should ensure that the process of ethical approval is standardised across Europe.

» Target audience: policy makers, regulatory authorities, medical professional organisations, research community.

4. Harmonise the implementation of Council Directive 2013/59/Euratom with respect to patient dosimetry within Europe.

Throughout the MEDIRAD project and from the answers to the Stakeholder questionnaire, it became evident that the implementation and interpretation of Council Directive 2013/59/Euratom [6] varies widely between countries and centres in Europe with respect to patient dosimetry. Sharing the expertise gathered in the context of the MEDIRAD project could contribute to regulatory development and help harmonise the implementation of these regulations across Europe.

» Target audience: policy makers, regulatory authorities, medical professional organisations.

5. Record radiation doses and treatment details in dose data repositories.

The studies conducted within MEDIRAD demonstrated that although data may be acquired and processed with different methodologies in different centres, similar results may be obtained. Radiation dosimetry may be further harmonised with the incorporation of uncertainty analysis, allowing a flexible approach to the acquisition of data and to dosimetry calculations. An imaging and dose data repository, the IRDBB, was developed within MEDIRAD to store image data, radiation absorbed doses, and ancillary information including electronic case report forms (see Annex 1). A similar database should be developed and maintained to collate patient-specific details, information relating to the treatments, and outcome data including quality of life.

Nuclear medicine and MRT procedures provide a suitable framework to assess the effects of low-dose radiation, due to the large number of patients treated each year throughout Europe and the ability to accurately calculate organ level absorbed dose and effective absorbed doses. Funding and resources should be made available to support a prospective epidemiological study which would inform the continuing debate concerning the validity of the linear-no-threshold method. In addition, a European database would offer the potential for application of AI and machine-learning techniques to interrogate the wealth of data that may be collected.

» Target audience: practitioners, policy makers, regulatory authorities.

2.3. MEDIRAD scientific achievements supporting recommendations

- Developed standard-operating-procedures for set up of centres for quantitative imaging of radioiodine.
- Set up of the first European network for quantitative imaging of radioiodine.
- Successful set up and running of a multi-national multi-centre study involving dosimetry in MRT.
- Development of an imaging and dose data repository for transfer of MRT imaging and dosimetry data.
- Identified a lack of medical physics support in smaller centres which are currently not set up to perform dosimetry in MRT.
- Identified differences in the implementation of Council Directive 2013/59/Euratom between centres and countries of the MEDIRAD consortium.

3

Breast cancer radiotherapy and secondary cardiovascular risks: Establishing risk models and identifying relevant biomarkers for improving clinical support and individual risk assessment.

Overall recommendation

Deploy a EU-wide strategy to better predict and reduce secondary cardiovascular risks in breast cancer patients treated with radiotherapy.

» Specific recommendations:

1. Use multivariable normal-tissue complication probability (NTCP)-models for cardiac toxicity in all breast cancer patients to identify those at risk of major radiation-induced cardiac events.
2. Continuously improve multivariable NTCP-models for cardiac toxicity on the basis of new data.
3. Set up a European prospective data registration programme.
4. Use cardiac imaging and circulating biomarkers for follow-up of early cardiovascular changes following breast cancer radiotherapy.
5. Conduct long-term longitudinal studies combining imaging and circulating biomarkers to develop successful preventive measures for radiation-induced cardiac toxicity.

3.1. Justification

Within the MEDIRAD project, two studies were conducted to identify patients at risk for radiation-induced cardiac toxicity and who may benefit from preventive measures.

Firstly, an international multi-center study (MEDIRAD-BRACE) was conducted to develop prediction models for cardiac toxicity based on pre-treatment variables and 3-dimensional distributions. The so-called normal-tissue complication probability (NTCP) models are used to predict the risk for individual patients of developing complications after radiation-based therapy, based on patient, disease, and treatment characteristics, including the dose distributions given to the healthy tissue surrounding the tumor. Besides informing patients about their expected risks of radiation-induced complications, NTCP models are clinically used to guide treatment decisions by looking at the difference in predicted risk of complications between treatment plans. The models developed in the BRACE study enable identifying breast cancer (BC) patients at risk of developing radiation-induced cardiac toxicity. To this purpose, a centralised and integrated clinical data and radiation dose repository was established from four European cancer centres, containing integrated data of over 6,000 breast cancer patients.

Secondly, an international multi-centre prospective cohort study (MEDIRAD EARLY-HEART) was conducted to discover early biomarkers of cardiac events after completion of radiation treatment, using blood and imaging biomarkers. The results from this study provide essential information for developing strategies for secondary preventive measures that can be tested in future projects.

The following science-based policy recommendations have been established in an effort to advocate and facilitate the establishment of a prospective data registration programme and a repository of clinical, dose and imaging data for BC patients undergoing radiotherapy at a European level, to enable continuous adaptation of prediction models as radiation technologies improve.

3.2. Implementation

1. Use multivariable normal-tissue complication probability (NTCP)-models for cardiac toxicity in all breast cancer patients to identify those at risk of major radiation-induced cardiac events.

Multivariable NTCP-models should be used by clinicians in all BC patients to identify those at risk of radiation-induced major cardiac events, including pre-existing risk factors at baseline, other treatment modalities, and cardiac radiation dose parameters.
BC patients with pre-existing risk factors for major cardiac events have an increased absolute excess risk to develop radiation-induced cardiac events already within the first five years after radiotherapy. Consequently, elderly BC patients are also at increased risk of radiation induced-coronary events.

A recent study with 910 BC patients who are also part of the BRACE cohort showed that radiation dose to pre-existing calcified atherosclerotic plaques in the left anterior descending coronary artery (LAD) is strongly associated with the development of acute coronary events [22]. Based on this BRACE subcohort, a preliminary mechanistic model of radiation-induced cardiovascular risk was developed that will be validated in the complete BRACE cohort. The results imply that, in patients with pre-existing advanced plaques, acute coronary events can already emerge within few years after radiotherapy.

With the availability of the NTCP-model, which is based on the mean heart dose, left ventricle V5, and pre-existing cardiovascular risk factors, it is possible to predict the risk of acute coronary events 10 years after radiotherapy for each individual BC patient, so that preventive measures can be taken or information on risk of cardiac complications can be provided accordingly. It is therefore recommended to apply NTCP-models for cardiac toxicity in all BC patients regardless of treatment site, boost, and/or inclusion of internal mammary chain or not.

» Target audience: regulatory authorities, medical professional organisations, research community.

2. Continuously improve multivariable NTCP-models for cardiac toxicity.

NTCP-models for cardiac toxicity should be continuously improved, as more data become available, for example when longer follow-up is available, cohorts become larger, or new radiotherapy or systemic treatments are introduced. Typically, these late side effects of irradiation increase with time of follow up. Larger (prospective) cohorts with longer follow up will enable to predict very long-term risks and to develop NTCP-models for subgroups of BC patients, e.g. younger and elderly BC patients, and BC patients with or without atherosclerotic plaques in the coronary arteries. Furthermore, radiomic features (other than the coronary artery calcium score) of the planning CT scans could be included.

Recently, it was confirmed that hypofractionated breast radiotherapy (26 Gy in five fractions over 1 week) is not inferior to the standard of 40 Gy in 15 fractions over 3 weeks for local tumour control [23]. This schedule may soon be the standard schedule for a large group of BC patients from European countries. It is therefore important to check whether NTCP-models for cardiac toxicity need to be updated when radiotherapy schedules based on fewer, larger fractions and lower total dose become standard treatment. Moreover, because of national/regional differences in patient population and treatment protocols, NTCP-models for cardiac toxicity may have to be finetuned as well.

» Target audience: research community.

3. Set up a European prospective data registration programme.

To enable improvement/updating of NTCP-models for cardiac toxicity, it is recommended to collect pre-treatment tumour and patient characteristics (including cardiovascular risk factors), treatment data, tumour status, dose distribution parameters, and cardiac events systematically

in each BC patient as part of lifetime routine follow up, preferably using a uniform and standardised prospective data registration programme. The European Particle Therapy Network (EPTN) has already developed the Proton International Research INSPIRE (www.protonsinspire.eu) infrastructure for standardised prospective data registration and this may also be used to collect high quality data for BC patients treated with photon therapy. Electronic Patient Reported Outcome Measures (PROMs) can be part of a centre's infrastructure to efficiently collect patient data at standardised time intervals.

» Target audience: regulatory authorities, medical professional organisations, research community.

4. Use cardiac imaging and circulating biomarkers for follow-up of early cardiovascular changes following breast cancer radiotherapy.

There is a need for precise knowledge on the relationship between radiation dose to specific cardiac structures and early subclinical cardiac changes that could eventually lead to cardiac complications.

The MEDIRAD EARLY HEART study has attempted to identify new cardiac imaging (based on echocardiography, cardiac CT, and cardiac MRI) and circulating biomarkers of radiation-induced cardiovascular changes arising within the first two years of BC radiotherapy [24]. Knowledge developed within EARLY-HEART can provide additional leads to improve early detection and prediction of cardiac events and should provide further insight on pathophysiological mechanisms. Results from this study complement those from the BRACE study.

» Target audience: medical professional organisations, research community.

5. Conduct long-term longitudinal studies combining imaging and circulating biomarkers to develop successful preventive measures for radiation-induced cardiac toxicity.

Imaging of cardiac damage and identification of circulating biomarkers is essential to unravel pathophysiological mechanisms of radiation-induced cardiac toxicity. Understanding the pathophysiology is essential for developing optimised radiation dose distributions aimed at reducing cardiac damage and subsequent cardiac events (primary prevention). Furthermore, targets may be identified for secondary preventive measures. Moreover, imaging and circulating biomarkers of subclinical cardiac damage may help to identify BC patients at high risk of future cardiac events and guide individualised cardiac screening programmes.

It is likely that different pathophysiological mechanisms play a role in radiation-induced cardiac toxicity at different time periods after radiotherapy, partly dependent on age of the patient and the presence of pre-existing cardiovascular risk factors. In this regard, follow up for two years after radiotherapy is still too short for unravelling the pathophysiological mechanisms based on imaging and circulating biomarkers of subclinical cardiac damage. Adding timepoints at 5, 10 and 25 years after radiotherapy to assess circulating and imaging biomarkers (echocardiography, cardiac MRI, and cardiac CT) will provide information on mechanisms that may come into

play later. Typically, these late side effects of irradiation increase with time of follow up, and correlation with earlier biomarkers could help to preventively treat patients at risk.

» Target audience: research community.

3.3. MEDIRAD scientific achievements supporting recommendations

- Multivariable NTCP-models to predict the risk for individual BC patients of developing acute coronary events were developed in BRACE study based on cardiac dose parameters and pre-existing cardiac risk factors.

- Our results show that these multivariable NTCP-models for cardiac toxicity need to be regularly updated with new data available and as radiotherapy techniques evolve.

- EARLY HEART study showed that specific markers from echocardiography, cardiac CT, cardiac MRI and circulating biomarkers have the potential to detect early cardiac changes arising within the first two years after BC radiotherapy.

- A study protocol combining EARLY HEART and BRACE studies would allow to detect early cardiac changes, follow their long-term evolution, and develop preventive measures accordingly.

4

Breast cancer radiotherapy and secondary cardiovascular risks: practical aspects on heart sparing.

Overall recommendation

Actively promote good practices aimed at reducing secondary cardiovascular risks after breast radiotherapy.

» Specific recommendations:

1. Utilise automatic segmentation tools to delineate the heart and its substructures.
2. Treat all left-sided breast cancer patients and right-sided breast cancer patients receiving radiotherapy of the internal mammary chain with deep inspiration breath-hold radiotherapy.
3. Consider proton therapy in cases of a clinically relevant estimated excess risk of acute coronary events, especially in younger patients.

4.1. Justification

Within the MEDIRAD project, an international multi-centre study (MEDIRAD-BRACE) was conducted to develop prediction models for cardiac toxicity based on pre-treatment variables and 3-dimensional distributions. The models developed in this study enable identifying breast cancer (BC) patients at risk of developing radiation-induced cardiac toxicity. To this purpose, a centralised and integrated clinical data and radiation dose repository was established from four European cancer centres, containing integrated data of over 6,000 BC patients.

The prediction models developed within the MEDIRAD-BRACE study contain dose parameters that are most predictive for the development of cardiac toxicity. This information is essential for the radiation oncology community to guide radiation dose optimisation in BC patients aimed at curing the cancer and preventing radiation-induced cardiac toxicity. The following science-based policy recommendations specifically address primary preventive strategies that radiation oncologists can implement.

4.2. Implementation

1. Utilise automatic segmentation tools to delineate the heart and its substructures.

It is advised to use an automatic segmentation tool to delineate the heart and substructures to prevent inter observer variation and hence generate more consistent cardiac dose volume histogram parameters (MHD and LV-V5) to calculate the individual absolute excess risk of acute coronary events. Furthermore, an automatic segmentations tool has the advantage of saving time.

» Target audience: medical professional organisations, research community, manufacturers.

2. Treat all left-sided breats cancer patients and right-sided breast cancer patients receiving radiotherapy of the internal mammary chain with deep inspiration breath-hold radiotherapy .

All left-sided BC patients should preferably be treated with deep inspiration breath-hold (DIBH). To spare treatment time, and spare patients the burden of DIBH when DIBH does not help in reducing cardiac dose, both a free breathing (FB) and DIBH planning CT scan can be made for treatment preparation. Right-sided BC patients receiving radiotherapy of the internal mammary chain can also benefit from DIBH radiotherapy as well as from a FB and DIBH planning CT scan for treatment preparation.

» Target audience: medical professional organisations.

3. Consider proton therapy in cases of a clinically relevant estimated excess risk of acute coronary events, especially in younger patients.

More advanced radiation techniques (such as protons) may be reserved for BC patients with a high absolute excess risk of radiation-induced acute coronary events based on advanced photon techniques (IMRT/VMAT). BC patients can be selected for protons based on a model-based planning comparison [25]. There should be a significant (predefined) reduction in absolute excess risk of acute coronary events as calculated with the NTCP-model (i.e. ≥2%) between the more advanced photon treatment plan and the proton plan to be eligible for treatment with the more advanced radiation technique.

When the absolute excess risk of acute coronary events is less than 2% with photons, no planning comparison has to be performed.
This way of selecting BC patients for proton therapy saves resources and will help to reduce the prevalence of radiation-induced cardiac toxicity.

» Target audience: medical professional organisations, research community.

4.3. MEDIRAD scientific achievements supporting recommendations

- The MEDIRAD BRACE study showed that the risk of acute coronary events afte BC radiotherapy increases with increasing dose to the heart. This excess risk can be determined by using the multivariable MEDIRAD-BRACE NTCP-model, which contains a number of dose volume parameters next to some baseline risk factor for acute coronary events.

- Using this NTCP-model, the risk reductions that can be obtained with more advanced radiation techniques can be calculated on an individual patient basis.

5

Modelling of patient dosimetry.

Overall recommendation

Accelerate the generalised use of modelled total delivered doses to individual patients in clinical practice within Europe.

» **Specific recommendations:**

1. Perform advanced assessment of the delivered dose in radiotherapy applications to improve and optimise treatment protocols for a personalised medicine approach.
2. Estimate patient-specific organ doses in diagnostic imaging applications, to allow better optimisation schemes.
3. Improve dosimetry of the total delivered dose outside the planning target volume in radiotherapy.
4. Determine and document patient organ doses in CT, interventional radiology and hybrid imaging.
5. Create databases using common nomenclature at the national and international level to facilitate personalised radiation therapy and diagnostic imaging.
6. Provide education and training on patient-specific dosimetry and the use of new technologies.
7. Better coordinate ongoing and new research initiatives in the field at the EU-level.
8. Promote research on quality and safety issues related to artificial intelligence in the field.

5.1. Justification

Artificial Intelligence (AI) will play a major role in the continuous effort to improve patient dosimetry, especially by providing solutions for fast and accurate dosimetric calculations, independently of the planned dose computed by the equipment. MEDIRAD research has shown that these solutions are close at hand. However, there are several challenges to overcome in order to

transfer research results to clinical everyday practise, ranging from the need for large transnational high-quality databases required for AI tools, machine learning, and deep learning, to the need for better coordination of the European research effort, and to improved education and training of clinical teams in this field.

5.2. Implementation

1. Perform advanced assessment of the delivered dose in radiotherapy applications to improve and optimise treatment protocols for a personalised medicine approach.

For personalised medicine, and patient-specific optimisation, it is necessary to assess the delivered dose to critical organs in radiation therapy, as this is the relevant dose to determine potential adverse acute and late effects. However, the currently documented planned radiation dose may differ significantly from that actually delivered. In nuclear medicine therapy, the current situation is even worse, since the estimation of the radiation dose to critical organs specific to each patient is still a challenge for many treatments.

MEDIRAD research has shown that accurate biokinetic modelling, and better molecular imaging data can be used to address this challenge. The knowledge obtained can be used to improve treatment protocols and optimise treatment for the individual patient in the context of a personalised medicine approach.

» Target audience: public health authorities, medical professional organisations, scientific communities.

2. Estimate patient-specific organ doses in diagnostic imaging applications, to allow better optimisation schemes.

Regarding the application of ionising radiation in diagnostics, MEDIRAD research has shown that organ dose values can be determined accurately by means of Monte Carlo methods and that those are related to image quality. Thus, it is feasible and important to determine and document patient-specific organ doses to verify the efficient use of the infrastructure. This would also be a cornerstone to allow better optimisation schemes for each individual patient. Today, patient indices are often used to document patient dose. This does not allow optimisations on an individual patient basis.

As for nuclear medicine examinations, generic models are still being used, with their inherent substantial uncertainties. The speed at which radiation dose in connection to the patient examination can nowadays be calculated, allows an easy implementation of individualised nearly real-time optimisation of diagnostic procedures for every single patient.

» Target audience: public health authorities, medical professional organisations, scientific communities.

3. Improve dosimetry of the total delivered dose outside the planning target volume in radiotherapy.

Improved dosimetry of delivered dose includes the need to derive and document radiation dose outside the planning target volume, since this is related to health effects such as cardiovascular effects. Radiation therapy protocols include a substantial amount of imaging to guide the treatments to optimise the irradiated volume. This imaging-related exposure increases the radiation to organs outside the planned target volume, which might contribute significantly to long-term radiation effects such as cardiovascular disease or secondary malignancies.

The importance of optimising these ancillary imaging protocols through a better documentation of related patient dose needs to be highlighted through education and training of radiation oncologists and other contributing health professionals.

» Target audience: medical professional organisations, medical practitioners.

4. Determine and document patient organ doses in CT, interventional radiology and hybrid imaging.

The radiation doses in CT, interventional radiology, and hybrid imaging approaches need to be determined and documented at the individual patient level. This is required by the EU BSS and will improve the data used for optimisation studies, as well as for epidemiological studies, in the future. Patient dosimetry at the patient level is today a major uncertainty in such studies. As stated above, this should be determined and documented as organ doses.

» Target audience: medical professional organisations, medical practitioners.

5. Create databases using common nomenclature at the national and international level to facilitate personalised radiation therapy and diagnostic imaging.

In order to perform a more personalised radiation therapy and diagnostic imaging, databases that can be read and used by other researchers must be created at the national and international level in a way that the standards of GDPR are met, so as to justify patients' trust in the legitimacy of use of their personal data. However, the generation of these databases might be seriously hampered by the variability of the national implementations of these GDPR regulations.

These issues are described under MEDIRAD Recommendation No. 1. Radiation dose data from hospitals are an important data input that need to be of high quality and reliability to contribute to optimisation or quality assurance. These data sets should consist of patient specifications as well as organ dose values or parameters from which such organ dose values can be derived as well as a systematic description of the medical procedure.

» Target audience: competent Authorities, medical radiation protection experts.

6. Provide education and training on patient-specific dosimetry and the use of new technologies.

Education and training courses on patient-specific dosimetry need to be established. The new approaches have to be understood and implemented in the clinics. The strengths and weaknesses of different approaches including their uncertainties have to be broadly understood. This is essential for the use and future use of the data. The new technologies provide the opportunity of a broad use of such personalised dosimetry, but these approaches are not always implemented and used in the hospitals. Education is needed, as well as hands-on training regarding theses aspects.

» Target audience: competent Authorities, medical radiation protection experts.

7. Better coordinate ongoing and new research initiatives in the field, at the EU-level.

Research in this field is ongoing in various areas. Different research initiatives are sometimes undertaken independently of each other. Ensuring the coordination of these initiatives will be greatly beneficial, especially in terms of quality assurance. A significant research effort is already underway in the area of patient-specific dosimetry for medical applications, but it needs to be better coordinated at the EU-level in order to provide maximised applicable results.

» Target audience: policy makers, scientific communities.

8. Promote research on quality and safety issues related to artificial intelligence in the field.

MEDIRAD has shown that individual patient dose assessment is feasible. The same holds for image quality assessment. For optimisation of therapeutic and diagnostic procedures at an individual patient level, this evolution in clinical practice should be as fast as possible. To allow that, AI-based methods for individual patient dosimetry and image quality assessment should be developed with a European perspective. This could be a first major step for the more general approach to use AI to optimise quality and safety issues in the medical use of radiation. Research in this field should therefore be strongly encouraged.

» Target audience: policy makers, scientific communities.

5.3. MEDIRAD scientific achievements supporting recommendations

- MEDIRAD research provided valuable insights regarding potential acute and late effects of healthy tissue exposure as well as dosimetric. evaluation in chest CT and PET/CT investigations.

- Using dedicated, varying sized, phantoms and patient models derived in a patient cohort, personalised dosimetry has been performed for CT exams based on Monte Carlo simulations and correlated to results from AI-based dosimetric evaluations. The AI approach showed very good results, even on a voxel scale approach, and can thus be used for medical treatment planning options and personalised dosimetry. A corresponding dose evaluation software tool for web-based use has been developed.

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6

Annex 1
Supporting evidence from MEDIRAD research.

1. Optimisation of image quality and dose in CT scanning, including CT in multimodality imaging and paediatric CT scanning

Novel Optimisation Methods in Chest CT.

A primary objective of the MEDIRAD project has been to optimise chest CT examinations through the development of a novel tool that, for the first time, can determine the optimal chest CT protocol through a fully integrated system that relates clinical indication, required image quality and lowest achievable patient radiation dose. To date, a dedicated method for evaluating organ doses for chest CT examinations has been developed. The scanner- and patient-specific Monte Carlo (MC) method has been shown to accurately estimate absorbed doses to irradiated organs during thoracic CT examination and is applicable to both paediatric and adult populations [7]. Objective image quality assessment methods to be used in real patient images and validated on the same image data sets have also been developed that are based on the characterisation and analysis of noise power spectrum (NPS) and modulation transfer function (MTF) [4], with regard for automatic tube current modulation (ATCM), automatic tube voltage selection (ATVS), and organ-based tube current modulation (OTCM) [8,9].

Additionally, image quality criteria based on clinically relevant structures have been identified by way of a Delphi consensus process and a subjective image quality assessment study using these structures is currently ongoing. The aforementioned methods that have been developed, combined with the final results of the subjective image quality assessment, will be integrated into a freeware modular software expert system [CT Image Quality and Radiation Dose (CT-IQU-RAD)] that will provide a) image quality information, b) accurate estimation of patient organ doses and c) estimation of radiogenic risk associated with chest CT examinations performed for several clinical indications.

Dose Evaluation and Optimisation in Multimodality Imaging.

The field of multimodality or hybrid imaging has seen rapid growth in the past decade, offering an effective means by which to diagnose and monitor disease at both the functional and molecular levels. However, CT protocols related to multimodality imaging are not often optimised leaving much room for improvement with regards to radiological protection within hybrid imaging. To gather information on the current use of multimodality imaging in nuclear medicine, and to provide a baseline for the availability and use of DRL values for CT examinations of this nature, a literature review was conducted and subsequently followed by an EU-wide survey [11].

From this work, it was determined that:

- Published national DRL values for CT acquisitions in nuclear medicine are scarce.
- CT scanning is most commonly used for attenuation correction and localisation rather than for diagnostic purposes.
- Substantial variation exists across different hospitals with regard to CT protocols and SPECT/CT and PET/CT systems.
- Currently there is a lack of paediatric specific CT protocols in nuclear medicine; and
- Increased education and training in CT technology and dosimetry is required, which could be achieved by addressing this topic in CME sessions of radiological and nuclear medicine conferences.

With the specific aim of establishing European DRLs for CT applications in multimodality imaging, an EU-wide patient dose survey was conducted in alignment with the recommendations established in ICRP Publication 135. Establishment of DRLs proved extremely difficult due to the challenges presented by subdivided datasets and the large variation in CT dose indicators and exposure levels. Despite these issues an initial set of DRL values have been proposed for localisation CT in half-body 18FDG PET, 99mTc-bone SPECT, and parathyroid SPECT as well as the first European DRL and achievable dose levels for attenuation correction CT in cardiac SPECT has been established.
Full reports on the current use of multi-modality systems in nuclear medicine and European DRLs for specific applications of CT in multi-modality systems can be accessed via the MEDIRAD website.

Radiogenic Risk.

Additionally, within the scope of Work Package 5, MEDIRAD is working to improve the direct estimation of cancer risk following low doses of ionising radiation from CT scanning in childhood and adolescence. By way of a cohort and nested case-control study, the role of factors which may modify cancer risk such as age, as well as genetic and epigenetic variants are being investigated. This work is ongoing and results will be integrated with the optimisation tools previously developed once available.

2. Patient specific dosimetry in molecular radiotherapy (nuclear medicine therapy)

The overall objectives of this sub-study within MEDIRAD were to develop and implement the tools necessary to establish, for the first time in a multicentre setting, the range of absorbed doses delivered to healthy organs in patients undergoing thyroid ablation and the threshold absorbed dose required for thyroid ablation. This would enable patient-specific treatment planning that will minimise the risk to the patient while ensuring a successful outcome.
The protocol for a future large-scale epidemiological study of the effect of low absorbed doses from the irradiation of normal organs by internal radionuclide sources was developed as part of MEDIRAD. This could potentially allow individualised risk/benefit treatment planning for these procedures. As a preparatory step for future clinical trials and studies, recommendations and protocols have been developed for the calculation of absorbed doses from internal [^{131}I]NaI sources.
To achieve these objectives, the following aims were identified:

- Gamma camera characterisation for high activity quantitative imaging to enable standardised collation of quantitative image data and absorbed dose calculations obtained at different centres.
- Dosimetry and kinetic modelling for 100 patients to establish the range of absorbed doses delivered to thyroid remnants and to normal organs from fixed levels of administered activity.
- To enable collation of absorbed does and outcome data a database was developed. The range of absorbed doses delivered to potential organs-at-risk were determined to enable the evaluation of short-and mid-term risk.
- These data will be used to develop personalised risk/benefit dosimetry-based treatment planning protocols as recommendations for best practice, whereby the therapeutic ratio can be optimised.

Within the scope of the MEDIRAD a multi-national multi-centre clinical study was set-up including quantitative imaging of radioiodine [131I]NaI and radiation absorbed dose calculations. Standardised site set-up protocols and imaging protocols were developed to allow the collation of quantitative imaging and absorbed dose calculations from four centres across Europe. This was a proof-of-concept study to highlight that multi-national multi-centre studies including a dosimetry component are feasible in molecular radiotherapy (MRT) and to show the wide-range of radiation absorbed doses delivered from administrations with standard activities.

The developed protocols and methodologies can be used for future studies to allow for quantitative imaging of high-activity radioiodine and for radiation absorbed dose calculations. Protocols were published by Taprogge et al [14]. The results have been published as publicly available documents on the MEDIRAD webpage as part of deliverables D3.1, D3.2, D3.3, D3.6, D3.8. Detailed guidelines and recommendations for quantitative [131I]NaI imaging and dosimetry are provided in D3.8.

Set-up of a European imaging network for quantitative [^{131}I]NaI.

A network of centres for standardised quantitative imaging of radioiodine was set-up comprising of four centres in three countries (UKW, UMR, IUCT-O and RMH). Further details of the developed protocols as part of MEDIRAD can be found in the publicly available deliverable 3.8 "Guidelines and recommendations for quantitative [131I]NaI imaging and dosimetry".

Multi-centre multi-national dosimetry study.

Ethics approval was granted to all investigating clinical centres of MEDIRAD by the respective ethics committees for an observational clinical study and recruitment of 100 patients across four centres was performed. MEDIRAD has set up the first multi-centre clinical study to measure absorbed doses to healthy organs for patients treated with radioiodine for thyroid cancer.

Participating research sites were required to have obtained ethical and management approval prior to opening for recruitment. As radiation protection regulations and laws differ between countries, the ethics approval process had to be performed in three countries. Delays in the ethics approval process and required changes in the protocol in one of the countries resulted in an overall delay of at least 1 year before recruitment could be started in each country. Furthermore, differences in the interpretation of the respective legislation and guidance resulted in the original protocol being denied ethics approval in one country, while it was accepted in other countries. A total of 100 patients were recruited with up to 5 SPECT/(CT) scans to perform dosimetry.

Dosimetry calculations.

SPECT images were quantified and corrected for dead time. WB, CT and SPECT DICOM images were anonymised and uploaded to a database, while retaining all header data describing the SPECT(/CT) system. These were required to apply the correct calibration factors. Throughout the process it was found that dosimetry calculations were only possible if the required DICOM header information was preserved; this required changes to the pseudo-anonymisation process and to the developed dosismetric bio-bank (IRDBB).

Dosimetry was performed for volumes-of-interest (VOIs) or on a voxel-by-voxel basis. For VOI-based dosimetry, the outlining techniques were well defined and were based on anatomical imaging in conjunction with visible uptake on the SPECT images. Dosimetry results from single time and multiple time point scans showed a range of maximum absorbed doses to the thyroid remnants from 0 to 150 Gy. Whole-body, lung and bone absorbed doses were < 0.1 Gy for all patients. Results from the study suggest a broad range of absorbed doses to the thyroid remnant.

Biokinetic modelling.

Bio-kinetic models published by the International Commission on Radiological Protection (ICRP) are based on measurements involving healthy, so-called reference, humans and animals [15,16]. These models are often not appropriate to estimate radiation doses for a specific patient cohort in nuclear medicine imaging or molecular radiotherapy [17]. Development of a patient-population specific pharmacokinetic model using actual patient data is important to compare the bio-kinetic properties to the established ICRP models and to potentially allow for patient-tailored treatment planning.

Feasibility of the modelling was assessed using retrospective data of 23 patients from a previous dosimetry study [18] for whom biokinetic data were available for thyroid remnant, blood, protein-bound-iodine and whole body. The modified ICRP-128 model (see Figure 1) was able to accurately reproduce the activity retention of the retrospective data. The modified model had slower transfer rate constants from blood to thyroid (0.12 day-1) compared to ICRP-128 (7.26 day-1). Thyroid to blood transfer in both models was found to be comparable (30 day-1 and 36 day-1). The model was subsequently further adapted using data acquired as part of the MEDIRAD multi-centre multi-national prospective studies.
The ICRP 128 bio-kinetic model was updated and a set of rate constants determined to accurately describe bio-kinetics of a thyroid cancer patient population. The developed model can be used for radiation protection assessments for this patient cohort. Furthermore, the model can potentially be used for personalised treatment planning to assess radiation doses to dose-limiting normal organs. For details see MEDIRAD deliverable D 3.7.

3. Breast radiotherapy and secondary cardiovascular risks: establishing risk models for clinical support, individual risk assessment

WP4 “Breast radiotherapy and secondary cardiovascular risks: establishing risk models for clinical support” of MEDIRAD project aimed to integrate clinical epidemiology, radiobiology, and modelling approaches to gain more insight into the mechanisms leading to radiation-induced cardiotoxicity in breast cancer (BC) patients and to develop and validate classical Normal Tissue Complication Probability (NTCP) and mechanistic models to relate doses to the heart to a variety of biological, subclinical and clinical endpoints.

WP4 aims to contribute to more accurate risk estimations for early and late radiation-induced cardiovascular biological and clinical events and thus provide potential targets for primary and secondary prevention.

Recommandations were based on two studies developed in MEDIRAD:

• MEDIRAD-BRACE aims to determine the relationship between 3D dose distributions in cardiac substructures and the risk of acute coronary events (ACE) and other cardiac complications in BC patients in order to develop an externally validated multivariable Normal Tissue Complication Probability (NTCP) model to assess the risk of ACE in individual patients based on cardiac dose metrics in the first 10 years after breast cancer RT. This is a retrospective study in in two parts: part one for model development (test cohort) and part two for external model validation (validation cohort). The test cohort is composed of 5,000 breast cancer patients treated at UMCG between 2006 and 2011.

The validation cohort is composed of 2,000 patients treated at the other 3 participating centres in the same period (IRSN, NKI, TUM-MED). The cohorts consist of female breast cancer patients treated with primary surgery, either by mastectomy or breast conserving surgery, and postoperative radiotherapy in the period 2005- 2010 and who were aged 40-75 years at time of RT start.

• MEDIRAD EARLY-HEART study aims to identify and validate new cardiac imaging and circulating biomarkers of radiation-induced cardiovascular changes arising within first 2 years of breast cancer radiotherapy and to develop risk models integrating these biomarkers combined with precise dose metrics of cardiac structures based on three-dimensional dosimetry. The EARLY HEART study is a multicenter, prospective cohort study in which 250 women treated for breast cancer and followed for 2 years after radiotherapy were included. Women treated with radiotherapy without chemotherapy for a unilateral breast cancer and aged 40-75 years met the inclusion criteria.

Baseline and follow-up data include cardiac measurements based on two-dimensional speckle-tracking echocardiography, computed tomography coronary angiography, cardiac magnetic resonance imaging, and a wide panel of circulating biomarkers of cardiac injury. The absorbed dose was evaluated globally for the heart and different substructures.

4. Breast cancer radiotherapy: Practical aspects on heart sparing

The MEDIRAD BRACE study showed that the risk of acute coronary events after breast cancer radiotherapy increases with increasing dose to the heart. This excess risk can be determined by using the multivariable MEDIRAD-BRACE NTCP-model, which contains a number of dose volume parameters next to some baseline risk factor for acute coronary events. Using this NTCP-model, the risk reductions that can be obtained with more advanced radiation techniques can be calculated on an individual patient basis.

5. Modelling of patient dosimetry at the voxel scale

To evaluate and understand the effects of medical exposures, focusing on two major endpoints with public health relevance: cardiovascular effects of low to moderate doses of radiation from either Chest CT or PET/CT investigations or in radiation therapy in breast cancer treatment including an understanding of mechanisms. The final expected objectives are better accounting of potential acute and late effects of healthy tissue exposure as well as dosimetric. evaluation in chest CT and PET/CT investigations.

Based on dedicated specific different sized phantoms and patient models derived in a patient cohort personalised dosimetry had been performed for CT exams based on Monte Carlo simulations and correlated to results from AI-based dosimetric evaluations. The AI approach showed very good results even on a voxel scale approach and can thus be used for medical treatment planning options and personalised dosimetry. A corresponding dose evaluation software tool for web-based use has been developed.

MEDIRAD

RECOMMENDATION 3

FURTHER OPTIMISATION OF RADIATION PROTECTION FOR PATIENTS AND MEDICAL WORKERS

PROJECT TITLE

Implications of Medical Low Dose Radiation Exposure

This project has received funding from the Euratom research and training programme 2014–2018 under grant agreement No 755523.

Introduction

MEDIRAD research has addressed the following three key aspects for the radiation protection of patients and of medical workers.

1. Setting up optimised systems for quantitative imaging of radiopharmaceuticals

This recommendation addresses the growing field of molecular radiotherapy (MRT) in nuclear medicine, focusing on improved radiation protection of patients through personalised treatment. The individual patient determination of pharmacokinetics and radiation dosimetry of established and innovative radiopharmaceuticals, greatly depends on the data provided by quantitative nuclear medicine imaging through gamma cameras, for which standardised protocols and performance are currently lacking. Characterisation of gamma camera performance for high activity quantitative imaging enables personalised treatment planning in MRT. It also enables standardised collation of quantitative image data and absorbed dose calculations to facilitate multi-national, multi-centre, clinical studies and to allow accurate absorbed dose estimations.

To achieve this, a number of challenges need to be addressed:

- Variability in methodologies to set up imaging systems for quantitative imaging and obtain calibration factors such as system volume sensitivity, partial volume recovery factors, and dead-time factors.
- Lack of guidance documents for quantitative imaging for different radionuclides.
- Lack of in-built capability and/or significant associated costs for additional software packages to allow for quantitative imaging.
- Lack of standardisation of imaging systems of different manufacturers.

To allow for quantitative imaging of radiopharmaceuticals and absorbed dose calculations, standardised protocols must be established, and this MEDIRAD recommendation proposes a way toward this goal.

2. Bridging medical communities

MEDIRAD research has highlighted how a closer cooperation between medical professionals can benefit the patient's radiation protection. Patients undergoing diagnostic and therapeutic procedures involving ionising radiation should receive care and follow-up from a multidisciplinary group of relevant specialists; especially in the case of adverse tissue reactions due to the radiation treatment. The multidisciplinary consortium of experts brought together by the MEDIRAD project, in radiology, radiotherapy and nuclear medicine, as well as in nuclear and radiation protection research has identified several avenues to ensure adequate and improved radiation protection of patients and medical personnel.

3. Radiation protection of medical workers in the field of interventional radiology

MEDIRAD research has focused on one of the exposure situations that accounts for a significant part of the collective dose received by medical professionals in European hospitals: the conduct of fluoroscopically-guided procedures in interventional radiology. Staff performing these procedures can be exposed to low doses of ionising radiations on a daily basis, eventually resulting in high doses throughout a complete career. The radiation field to which staff are exposed is highly heterogeneous, resulting in some body parts being more exposed than others. In general, workers wear at least a lead apron that partially protects most organs in the trunk, but other parts of the body can be unprotected, such as the skin of the hand and fingers which are usually close to the X-ray beam during most procedures.

Additionally, there has been increasing concern in recent years regarding exposure of the eye lens and brain, highlighting the need for optimising staff protection. Innovative protection devices have appeared on the market but the current European regulation does not provide practical criteria to support medical physicists and radiation protection experts in the selection of these devices. The EURATOM 2013 European directive simply states the need for providing, testing and checking "appropriate personal protective equipment", while the regulation on personal protective equipment underlines the selection of "the type and equivalent thickness of the constituent material(s) suitable for the foreseeable conditions of use", "without leading to an increase in exposure time as a result of the impedance of user gestures, posture or movement". Further, the general requirements in the international standards on, among others, the properties of the materials and the equipment themselves, are not sufficient to ensure effectiveness in clinical practice.

As a result, the use of such protective equipment is not as common as it should ideally be. MEDIRAD research identified that increased independent testing of such equipment, with reference to typical and realistic conditions of use, would be an effective way to promote better radiaiton protection practice for the medical workers concerned.

1

Setting up optimised systems for quantitative imaging of radiopharmaceuticals.

Overall recommendation

Optimise systems for quantitative imaging irrespective of camera make or model.

» **Specific recommendations:**

1. Establish a roadmap to enable personalised treatment planning on any imaging system and to benchmark quantitative imaging capabilities across centres.
2. Provide necessary funding and medical physics support to allow for quantitative imaging and radiation dosimetry in all clinical centres offering molecular radiotherapy.
3. Establish a dialogue between competent authorities, manufacturers and medical physics experts to ensure imaging systems can be effectively enabled for quantitative imaging.
4. Enable smaller centres to participate in multi-centre dosimetry trials by providing funding for support from medical physics experts.
5. Ensure that radionuclide calibrators used for molecular radiotherapy (MRT) are traceable to an appropriate national primary standard.

1.1. Justification

The science-based policy recommendations above were developed to advocate and facilitate the further development of European-level protocols for quantitative imaging of radiopharmaceuticals, including site set-up measurements, and imaging protocols, for the improvement of patient radiation protection.

The recommendations are based on work with [^{131}I]NaI, the most widely used radiopharmaceutical in molecular radiotherapy, but could easily be amended for other radiopharmaceuticals.

These recommendations, which aim to answer the expectations of MEDIRAD Stakeholders, are based on the research results and experience gathered in the MEDIRAD project.
They are intended for policy makers, public health authorities, medical professional organisations, as well as medical personnel involved in the imaging and absorbed dose calculations in MRT. They are designed to facilitate the widespread roll-out of quantitative imaging in nuclear medicine and MRT in order to allow for absorbed dose calculations, as required under Council Directive 2013/59/Euratom.

1.2. Implementation

1. Establish a roadmap to enable personalised treatment planning on any imaging system and to benchmark quantitative imaging capabilities across centres.

While standardised protocols are the first step towards quantitative imaging at centres, their implementation can be perceived by some centres as a time-consuming and challenging process due to differences in imaging systems and software packages used for the absorbed dose calculations. To allow for standardised quantitative imaging and absorbed dose calculations in MRT, a roadmap should be developed by public health authorities, medical professional organisations, and the scientific community, involving the manufacturers of imaging systems, to enable personalised treatment planning on any imaging system.

Further, as is standard practice for external beam radiotherapy, support for medical physics experts, and reimbursement for routine clinical dosimetry calculations, is needed for personalised treatment planning including dosimetry. Furthermore, work performed by MEDIRAD suggests that global calibration factors may be used for the same manufacturer and model of a gamma camera if standardised image acquisition and reconstrunction protocols are employed.

» Target audience: health authorities, medical professional organisations, scientific communities, manufacturers.

2. Provide necessary funding, and medical physics support, to allow for quantitative imaging and radiation dosimetry in all clinical centres offering molecular radiotherapy.

Participation in multi-centre, multi-national, clinical studies in MRT with a dosimetry component necessitates standardisation of quantitative imaging in each centre. Currently, there is a lack of positions for experts in medical physics who are essential for performing dosimetry estimations. Therefore, a pipeline supply of suitably qualified medical physicists, with a comparable level of training throughout Europe, is required.

The protocols developed within MEDIRAD will allow centres to be enabled for [131I]NaI quantitative imaging, and may be adapted to other radiopharmaceuticals.

» Target audience: medical professional organisations, medical practitioners, scientific communities, health authorities.

3. Establish a dialogue between competent authorities, manufacturers, and medical physics experts to ensure imaging systems can be effectively enabled for quantitative imaging.

MEDIRAD has shown that the set up of imaging systems for multi-centre, multi-national, studies is possible, but that measurements remain complicated and time consuming due to different national/local radiation protection regulations and differences in gamma cameras depending on the manufacturer. Further coordination between competent authorities, manufacturers, medical physics experts, and radiation protection experts is needed to ensure a standardised set up of systems across Europe to allow large-scale, multi-centre, multi-national, clinical studies in molecular radiotherapy to be conducted.

» Target audience: competent authorities, manufacturers, medical radiation protection experts.

4. Smaller centres should be enabled to participate in multi-centre dosimetry trials by providing funding for medical physics expert support.

Medical physics support at each centre is crucial to allow for the set up of centres and their imaging systems for quantitative imaging. Centres with limited medical physics support may, potentially, be curently unable to participate in clinical studies that require quantitative imaging due to the significant efforts required to set up imaging systems. Furthermore, EC Directive 2013/59/Euratom article 56 states that exposures of target volumes in nuclear medicine treatments shall be individually planned and their delivery appropriately verified. Only centres with sufficient medical physics support are able to adhere to this directive. Funding should be made available for centres to have access to sufficient medical physics expert support to enable quantitative imaging and absorbed dose calculations.

» Target audience: policy makers, scientific communities.

5. Ensure that radionuclide calibrators used for MRT are traceable to an appropriate national primary standard.

Traceable image quantification is an essential requirement for multi-centre clinical studies and is necessary to make quantitative imaging and radiation dosimetry results comparable between centres. Furthermore, if results of multi-centre MRT clinical studies are to be adopted for routine clinical practice, each centre must ensure that image quantification is performed in a comparable and traceable manner.

The site set up measurements of [^{131}I]NaI in the multi-centre clinical study performed by MEDIRAD have shown that traceability to a national primary standard was not always easily achievable: dose calibrators in that study were either traceable to a national standard or had calibration certificates from an accredited laboratory. In one centre the accuracy of the dose calibrator was assessed with respect to a local standard.

» Target audience: policy makers, scientific communities, competent authorities, medical radiation protection experts.

1.3. MEDIRAD scientific achievements supporting the above recommendations

- Developed standard operating procedures for the set up of centres for quantitative imaging of radioiodine.
- Successfully set up and conducted a multi-national, multi-centre, study involving dosimetry in molecular radiotherapy.
- Set up of the first European network for quantitative imaging of radioiodine.
- Results suggest that gamma cameras of the same make and model show very similar response to radioiodine and that the set up process can be simplified.
- Developed a dose data repository for the transfer of molecular radiotherapy imaging and dosimetry data.
- Identified a lack of traceability across Europe which will impact the accuracy and comparability of results.

2

Bridge medical communities to improve radiation protection.

Overall recommendation

Encourage harmonisation of practices through active engagement between health professionals, researchers, health authorities, and patients.

» **Specific recommendations:**

1. Establish multidisciplinary protocols of care for high risk procedures, including guidance on pre-procedure planning, intra-procedure strategies, and post-procedure follow-up, and integrate into quality management systems.
2. Draft and implement guidance documents on justification of diagnostic / interventional / therapeutic procedures to facilitate effective, and streamlined, communication between the disciplines involved in patient care and follow-up.
3. Encourage the development of Artificial Intelligence (AI) applications, to integrate multidisciplinary information and facilitate patient's follow-up.
4. Provide tailored and standardised continuous education and training for medical professionals on radiation protection and optimisation.
5. Engage with the public, and patients in particular, by informing, listening and developing a robust communication strategy and educational materials developed in consultation with patient associations.

2.1. Justification

The scope of this recommendation is to enhance awareness among medical professionals (including those outside the radiology, nuclear medicine, and radiotherapy professions) and scientific communities of the importance of interdisciplinary connections for optimising radiation protection and to promote efforts which facilitate this new way of conducting medical research.

Specifically, the recommendations herein aim to overcome current barriers to transdisciplinary optimisation of radiation protection and propose ways in which to bridge medical communities for the improved protection of patients and workers. Such cooperation and engagement can be facilitated by joint programming and calls for research focused on radiation protection implementation in clinical practice.

2.2. Implementation

1. Multidisciplinary protocols for high risk patient procedures should be established. The protocols should provide guidance for pre-procedure planning, intra-procedure strategies, and post-procedure follow-up, and should be integrated into quality systems.

Attention has to be paid to minimise patient exposure. The complexity of procedures requires a multidisciplinary approach that involves the specialist doctor, the specialist in medical physics, the radiographer, and the nurse. Collectively these professionals form a team committed to optimising the radiological technique, the clinical procedure, and the performance of the radiological equipment. If needed, this should also include medical professionals outside traditional radiology groups, e.g. dermatology, primary care physicians, etc.
This is in compliance with ethical principles but also Euratom Directive 2013/59 which requires that, without prejudice to competences and responsibilities of the various professional figures, the exposure of the patient is optimised and as minor as possible while remaining compatible with the achievement of the diagnostic or therapeutic purpose in case of procedures requiring radiological imaging guidance. Multidisciplinary protocols should be set up for high risk patient procedures and they should mainly deal with:

- Informed consent and information to the patient with reference to medical ionising radiation exposure and, for repeated and complex procedures, the potential risks of skin damage.
- Patient exposure monitoring, dose assessment methods to organs, methods of skin exposure monitoring, and patient follow-up after complex high-dose procedures.
- Exposure optimisation methods, description of the technical parameters that influence the dose to the patient, optimisation of the clinical protocol, discussion of the complexity of the procedures, and the periodic monitoring of exposure methodology through the comparison with relevant diagnostic reference levels (DRLs).
- Management of equipment: description of the salient features, methods and contents of a quality assurance programme, including quality controls, which are necessary to guarantee the maintenance of system performance over time.

Performance against these protocols should be incorporated into organisational quality management systems.

» Target audience: practitioners, medical professional organsations, research community.

2 Implement / draft guidance documents on the justification of diagnostic / interventional / therapeutic procedures to facilitate effective, and streamlined, communication among the various disciplines involved in patient care and follow-up.

It has been foreseen by the MEDIRAD Consortium and Stakeholder Forum, and witnessed through various European-level research initiatives, that a standardised approach to clinical practice and quality assurance must be implemented for effective and efficient interdisciplinary communication. The need to improve compliance to the principle of justification arises directly from the changing patterns of practice in diagnostic radiology, particularly the routine introduction of relatively high-dose techniques. It is recommended that medical professionals and the research community develop procedure-specific guidance documents for the justification of diagnostic / interventional / therapeutic techniques and patient pathways.

In this way, clinical practice and workflow can be better harmonised for ease of collaboration and best practices for the protection of patients and workers maintained. Development and implementation of common guidance documents on the principle of justification would be facilitated by raising awareness through communication and consent, by sharing appropriateness criteria as referral / acceptability guidelines, and by implementing clinical audits on justification. Harmonisation of guidance documents could avoid divergent interpretations and risk of duplication.

» Target audience: practitioners, medical professional organisations, research community.

3. Encourage the development of Artificial Intelligence (AI) applications to enhance radiation protection by means of bridging multidisciplinary information and facilitating patient follow-up.

AI could help manage, predict, and even reduce patient exposure to ionising radiation. Every field within the scope of medical ionising radiation is looking at the opportunities offered by AI to advance imaging and radiotherapy's contributions to healthcare. AI applications are suitable for diagnosis, treatment planning, and follow-up analysis, with strong potential impact on personalised medicine. AI could also be used to predict, rather than measure, dose during an intervention, which would improve the safety of said intervention.

AI could represent a bridge between medical communities, as well as benefit from the data and multidisciplinary expertise of the different disciplines. In fact, the intent of this "bridging" is to proactively identify, monitor, and improve a range of medical, environmental, and social factors relevant to the health of communities. These efforts show a significant growth in a range of population health-centric information exchange and analytics activities. Improvement in diagnostic image quality (for a given dose) can be achieved, for example, by the use of AI processing models combined with the definition and implementation of AI trained task-specific observers which provide quality information beyond the conventional quality indices. The overall system requires a strong collaboration between algorithm developers, medical physicists, radiologists, and radiographers.

AI applications in medical imaging, nuclear medicine, or radiation oncology, require close interaction among medical physicists, radiologists, nuclear medicine physicians, cardiologists, radiation oncologists, and radiographers. They should set up a national network among health research structures and scientific societies to share standardised collected data, to extract the informative content of the data, through the use of dedicated algorithms. Sharing can be performed at different levels; edge computing and federated learning platforms are gaining interest in terms of sustainability and sensitive data protection requirements. A promising domain for AI applications in radiation protection deals with scatter reduction, denoising, and image reconstruction methods. Another attractive option is to exploit AI-based approaches in order to improve managing, and adjusting, dose to individual patients: it can be anticipated that it will be possible in the near future to quantify image acquisition parameters and optimise procedures before or during each examination, evaluating image quality in real-time for a given patient.

» Target audience: practitioners, medical professional organisations, research community.

4. Tailored and standardised continuing professional development of supported and resourced education and training programmes for medical professionals on radiation protection and optimisation, should be foreseen.

Aligned with Article 18 of Council Directive 2013/59/Euratom, it is critical that all practitioners and clinical research staff involved in any practical aspect of medical ionising radiation undertake continuous education and training on radiation protection aspects relevant to their specific area of work. European core curricula should be tailored for all professionals involved in radiation sciences, while promoting interdisciplinary collaboration.

Additionally, these curricula must undergo regular review to stay up to date with ongoing advancements in technology, techniques, and best clinical practices. It is recommended that the Council of the European Union, and relevant policy makers, provide detailed guidance documents regarding implementation and regular revision of continuing professional development (CPD) programmes in radiation protection to best ensure frequent, robust, and standardised education and training for all those involved in the medical use of ionising radiation. It is essential that such systems are supported and resourced at a national level.

» Target audience: policy maker, regulatory authorities, medical professionals, research community.

5. Education and training of the public, and in particular patients, to make them fully informed, and their opinion taken into account, by way of robust communication strategies and educational materials developed in consultation with patient associations is needed.

It is important to bridge the gap between patients and care providers and it has become widely accepted that patient understanding and consent around medical treatment are critical for the protection of public health and well-being, including radiation protection. Yet recent research has demonstrated a notable lack of public knowledge and proper informed consent formulation in the medical ionising radiation sector.

The development of education and training for the general public should take into account previous research and have regard for existing organisations dedicated to improving public knowledge.
Medical professional organisations and practitioners, in collaboration with patient associations, are encouraged to further develop communication strategies and patient-centred educational material (e.g. leaflets, posters, short videos, analogies, etc.) regarding the equipment/technology, justification, benefits and risks of ionising radiation. Additionally, the research community should look to disseminate research findings via communication channels with a strong patient interface, similar to what MEDIRAD has worked to achieve through collaboration with EuroSafe Imaging. All essential best practice elements (e.g. benefit-risk communication, risk management, etc.) need to be integrated.

» Target audience: medical professional organisations, practitioners, patient associations, research community.

2.3. MEDIRAD achievements supporting recommendations

- MEDIRAD brought together a multidisciplinary research group from different areas of medical research and clinical practice to achieve project objectives.
- A Stakeholder Forum (SF) was set up which facilitated regular consultation with an inter-disciplinary group of healthcare professionals, medical professionals, scientists, policy-makers, industry partners, and competent authorities. Consultation took place throughout both project development and execution.
- Linking medical professionals from relevant disciplines was identified by the SF as a key factor for the optimisation of patient follow-up.
- The SF highlighted a lack of education and training, in some subject areas, related to radiation protection optimisation for some professional groups.
- Through discussions with the SF and project leaders, the need for greater patient/patient association engagement in radiation protection research was highlighted along with the need to make patients and the general public more aware of the benefits and risks of ionising radiation and the importance of patient involvement in research. .
- Project leaders identified the need to create guidance documents on the justification of diagnostic/interventional procedures along with patient/pathology-tailored protocols for high risk procedures.
- MEDIRAD has provided valuable resources to support and inform the development of such guidance documents or protocols. Resources include: risk models; standardised protocols; Image and Radiation Dose Biobank (IRDBB); software tool (CT-IQURAD) modules on image quality and radiation dose.

3

Optimisation of radiation protection of medical workers.

Overall recommendation

Optimise the use of protective equipment to improve radiation protection of medical workers in interventional settings.

» **Specific recommendations:**

1. Support the development of appropriate guidance at European-level in order to facilitate reduction of staff exposure through good practise.
2. Encourage continuous education of medical professionals, including appropriate information related to radiation shielding equipment.
3. Encourage independent testing of equipment performance in typical conditions of use.
4. Support the use of protective equipment in daily clinical practise.

3.1. Justification

MEDIRAD explored the performances of shielding protective equipment selected for their novelty, their widespread use, and/or their potential for dose reduction in the context of interventional radiological procedures for workers. The research confirmed that, in many exposure conditions, the use of such equipment may contribute significantly to improved protection whereas other equipment could become nearly ineffective in other exposure conditions.
These contrasting results underline the need to carefully select the protective devices and consider the actual conditions of use. This could most effectively be implemented through existing, and future, standards, and through professional guidance.

In particular, the effectiveness of following equipment was investigated:

- Lead and lead-free caps
- Leaded masks
- Lead and lead-free drapes
- Light lead and lead-free aprons
- Zero-gravity suspended system

Detailed recommendations and supporting results are available in Annex 2. To complete the recommendations, literature data were gathered for:

- Ceiling-suspended screens
- Lead glasses

Their effectiveness was investigated by combining three complementary methods: Monte Carlo (MC) simulations, measurements on staff, and measurements on anthropomorphic phantoms. Particular attention was given to potential dose reduction to the eyes and the brain due to the current International Commission on Radiological Protection (ICRP) thresholds for tissue reactions. Although the equipment effectiveness was investigated for procedures and configurations frequently used in interventional cardiology practice, the results should apply to other specialities provided the configurations and irradiation conditions are similar.

3.2. Implementation

1. Support the development of appropriate guidance at the European-level to reduce staff exposure through good practise.

As the actual contribution of shielding equipment to the dose reduction to workers might strongly depend on factors related to their conditions of use, appropriate guidance should be produced at the European-level in order to facilitate the exposure optimisation through good practise. Such guidance could be produced in cooperation between end-user professionals, radiation protection experts, and equipment manufacturers.

» Target audience: policy makers, regulatory authorities, research community, professional societies, practitioners, hospital managers.

2. Encourage continuing education of medical professionals, including appropriate information related to radiation shielding equipment.

Training curricula should be organised for the education of medical professionals, as per the European Commission guidelines. These curricula should include up to date and appropriate information related to available, and technically-proven, shielding equipment. The habits of the medical professionals regarding the use of radiation protection equipment in daily clinical practice, and how it affects shielding effectiveness, should also be reviewed.

» Target audience: policy makers, regulatory authorities, research community, professional societies, practitioners, hospital managers.

3. Encourage independent testing of equipment performance in typical conditions of use.

Independent testing of radiation shielding equipment shows that the effective performances in typical conditions of use are usually lower than could be assumed from the material properties as observed in lab conditions. This is very dependent on how the protective equipment is used and on the specifics of the procedure. Also, the attenuation characteristics as stated on the equipment label are indicative of the lead equivalence of the material or the resulting X-ray attenuation in a direct X-ray beam with a specific energy spectrum, which might not be representative of the dose reduction to any specific organ. In addition, the availability of the composition of lead-free material would help to estimate their performance in different exposure conditions.

For the optimised protection of medical professionals, independent testing of the key performance characteristics of shielding equipment, including their ease of use, should be encouraged, in line with the EURATOM Directive requirements. In particular, collaboration between professional societies as well as medical professionals is desirable since independent testing can be very demanding in terms of time, knowledge, and equipment. An update of standards related to such equipment might be necessary, to reflect that specific requirements of current standards and certifications are not sufficient to ensure practical effectiveness.

» Target audience: policy makers, regulatory authorities, research community, practitioners, hospital managers.

4. Support the use of protective equipment in daily clinical practise.

For optimal radiation protection, protective equipment should be readily available to the medical professionals in daily clinical practise. They should also receive adequate support to ensure that the radiation protection equipment is optimally used in practise.

» Target audience: practitioners, hospital managers.

3.3. MEDIRAD scientific achievements supporting recommendations

- Evaluation of effectiveness of five pieces of protective equipment by means of computer-aided simulations.
- Validation of simulation results by means of clinical measurements on staff and on phantoms.
- Results confirmed that: (i) the tested equipment may significantly improve staff protection in many exposure conditions, but (ii) could become ineffective in adverse conditions.
- Results underline the need for careful selection of the equipment taking into account the actual conditions of use.
- Identification of the inadequacy of lab measurements to predict the effectiveness of protective equipment in clinical conditions.

4

Annex 1
Supporting evidence from MEDIRAD research.

RECOMMENDATION 3.1

Protocols to set up optimised imaging systems for quantitative imaging of [^{131}I]NaI irrespective of camera make or model

MEDIRAD Scientific Goals and Research Results

Within the scope of the MEDIRAD a multi-national multi-centre clinical study was set-up including quantitative imaging of radioiodine [^{131}I]NaI. This was a proof-of-concept study to highlight that multi-national multi-centre studies including a dosimetry component are feasible in molecular radiotherapy (MRT). The developed protocols can be used for future studies to allow for quantitative imaging of high-activity radioiodine.
Protocols were published by Taprogge et al (1). The results of MEDIRAD have been published as publicly available documents on the MEDIRAD webpage as part of deliverables D3.1, D3.2, D3.3, D3.6, D3.8. Detailed guidelines and recommendations for quantitative [^{131}I]NaI imaging and dosimetry were provided in D3.8.

Setup of a European imaging network for quantitative [^{131}I]NaI

A network of centres for standardised quantitative imaging of radioiodine was set-up comprising of four centres in three countries (UKW, UMR, IUCT-O and RMH). Five SPECT(/CT) systems at the four centres were calibrated with respect to their system volume sensitivity, recovery coefficients and dead-time. All results have been published by Taprogge et al. (1) including details of the proposed site set up protocol for quantitative imaging of [^{131}I]NaI. Further details of the developed protocols as part of MEDIRAD can be found in the publicly available deliverable 3.8 “Guidelines and recommendations for quantitative [^{131}I]NaI imaging and dosimetry”.

The site set-up protocol developed for quantitative imaging of [^{131}I]NaI is presented in "Annex 1 - Protocol for the set-up of a European imaging network for quantitative [^{131}I]NaI".

Methodologies for standardised pre-study gamma camera set-up and calibration measurements were in part defined by restrictions based on the local interpretation of radiation protection laws in different countries, which for example prevented the use of large quantities of liquid [^{131}I]NaI. Site set-up measurements were performed according to National Electrical Manufacturers Association (NEMA) standards wherever possible (3). Accuracy of ancillary equipment in the quantification chain was also assessed as part of the process including clock synchronisation, traceability of radionuclide calibrators and accuracy of weighing scales. Radionuclide calibrators used must be traceable to an appropriate national primary standard. (4)
Results of the MEDIRAD site set-up measurements in conjunction with results published by Gregory et al. (5) indicate that the use of global calibration parameters for cameras of the same make and model may be justified. This will facilitate the extension of the imaging network for further dosimetry-based studies.

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Protocol for the setup of a European imaging network for quantitative ^{131}I Preparing for the Setup Visit

The pre-study site setup measurement will consist of calibration measurements of the gamma cameras at each site. The aim is to optimise and standardise image data collected from each participating centre.

In preparation for the setup visit please ensure the following checks have been made.

Table 1
PRE-CALIBRATION QUALITY ASSURANCE TESTS

Test	Within preceding	Limits
Photopeak position	Month	Centred within peak energy window defined in Table 2
^{131}I intrinsic (20 Mcount) uniformity	Month (allow time to correct artefacts where necessary)	Integral CFOV ≤ 4% Differential ≤ 3% NO MAJOR TUBE ARTEFACTS
^{131}I intrinsic (20 Mcount) uniformity at high count rates (~100 kcps)		
^{99m}Tc intrinsic (20 Mcounts) uniformity		
Centre of rotation for High-Energy General Purpose (HEGP) collimators	Month	Within local limits
SPECT/CT system alignment, if applicable	Month	
Extrinsic HEGP flood	Month	
QC of weighing scales used in these measurements	Year	
QC of dose calibrators used in these measurements	Day	

Please note:
Before making these calibrations all centres need to check with the camera manufacturers that their system are set-up to acquire at high count rates of ^{131}I.

SPECT Acquisition Protocols

Please save the patient imaging protocols on the gamma camera with the parameters given in Table 2. These will be used for the following calibration measurements and patient scans. It is important that the parameters used to acquire patient data match those used for these calibration measurements.

Angular sampling at 6°, with 60 projections, has been chosen to achieve better statistical quality projections and reduce the noise introduced by triple-energy window (TEW) scatter correction. Noisy, low count rate projections can lead to biases in quantification due to the non-negativity constraint of Ordered-Subset Expectation-Maximisation (OSEM).

Preliminary measurements have been made to ensure that this makes negligible difference to the spatial resolution or visualisation of the smallest (1 cm diameter) calibration sphere, compared to 3° angular sampling.

Table 2
^{131}I PATIENT SCANNING PARAMETERS

Parameter	Suitable for ^{131}I
Collimator	HEGP
Photopeak energy window (20%)	364 keV ± 10%
Low scatter energy window (6%)	318 keV ± 3%
High scatter energy window (6%)	413 keV ± 3%
WB planar	
Acquisition mode	Continuous
Speed	20 cm/min*
SPECT(/CT)	
Matrix	128×128
SPECT movement	Body contour (or radius as close to phantom as possible)
Projections	60 (6° projection)
Time per projection	60 s*
CT	Standard low-dose protocol

* Acquisition duration will be adjusted according to the count rate.

Table 3
EXAMPLE SPECT IMAGE RECONSTRUCTION PARAMETERS

Parameter	Suitable for ^{131}I
Reconstruction	OSEM
Attenuation correction (AC)	CTAC if available, otherwise Chang (0.11 cm^{-1} @ 364 keV)
Scatter correction	Triple-energy window (TEW)
Iterations and subsets	4 iterations, 10 subsets
Post-reconstruction filtering	None
Resolution recovery	No

This number of iterations has been shown to reach convergence of the smallest sphere for Hermes Monte Carlo based scatter correction reconstructions. This may need further optimisation at each centre depending on acquisition hardware and reconstruction software. For Siemens Symbia based reconstructions make sure that the 'Preserve Low Count Data' option is NOT checked, as this, and the resolution recovery feature multiplies the counts up by an arbitrary value.

Suggested Site Visit Plan

The initial site set-up measurements could be performed over a single day; a total of 4 hours system time per gamma camera is needed to perform these measurements. Additional scanning of the DT phantom every 24–192 h for eight weeks will be required. Checking protocols and preparing phantoms will take an additional couple of hours. The phantoms filled with liquid ^{131}I will need to be stored on-site whilst their activity decays. Please ensure that there are appropriate storage facilities for the phantom used to determine system volume sensitivity for at least six weeks, and that the phantom

will not be required for anything else in that time. The spheres and lesions used in the recovery coefficient measurement and validation will also need to be stored for at least nine weeks before they can be emptied and sent to the next centre as exempt packages.

^{131}I SPECT Calibration Factor Measurement

Calibration factors are needed to correct for partial volume and resolution effects on the activity concentration measured in the reconstructed SPECT images. This is necessary to ensure quantitative accuracy of the images used for dosimetry. It is important to measure the activity concentrations of the spheres imaged in this calibration as accurately as possible.
These measurements should be performed only after recent intrinsic uniformity, peak checks, centre of rotation and SPECT/CT alignment checks. Extrinsic 57Co floods should have been acquired recently to ensure the collimator integrity.

Prepare Solution

Equipment:

- 150 MBq liquid ^{131}I
- Radionuclide calibrator with factors for ^{131}I traceable to the national primary standard
- 1 g potassium iodine and 1 g sodium thiosulphate
- Perspex shell of IEC head phantom
- Custom lid with 3D printed sphere inserts
- Large gauge spinal needle
- Bench cote / inco pad & micropore
- Approximately 1 h scan time

Table 4
SPHERE INSERT DIAMETERS AND VOLUMES

Internal diameter (cm)	Volume (ml)
1.0	0.524
1.7	2.57
2.8	11.5
3.7	26.5
5.0	65.4
6.5	144

Procedure:

1. Zero the scales and weigh the empty 500 ml bottle (with lid).
2. Weigh 300 ml of water into the bottle and add the potassium iodine and sodium thiosulphate and agitate.
3. Weigh empty vial.
4. Dispense 150 MBq into the vial and top-up volume to 4 ml.
5. Weigh full vial.
6. Measure the vial activity in the calibrator using the correct factor.
7. Draw up and wash out the contents of the vial into the bottle.
8. Reweigh the full bottle (with lid).
9. Measure the residual vial and syringe activity in the calibrator. The residual activities should be negligible.

Prepare the Phantom

Procedure:

1. Attach the spheres to the modified IEC phantom lid in the configuration shown in Figure 1 below.
2. Fill the phantom with water and secure lid.
3. Fill the 1.0, 1.7 and 2.8 cm diameter spheres with the ^{131}I solution, avoiding air bubbles.

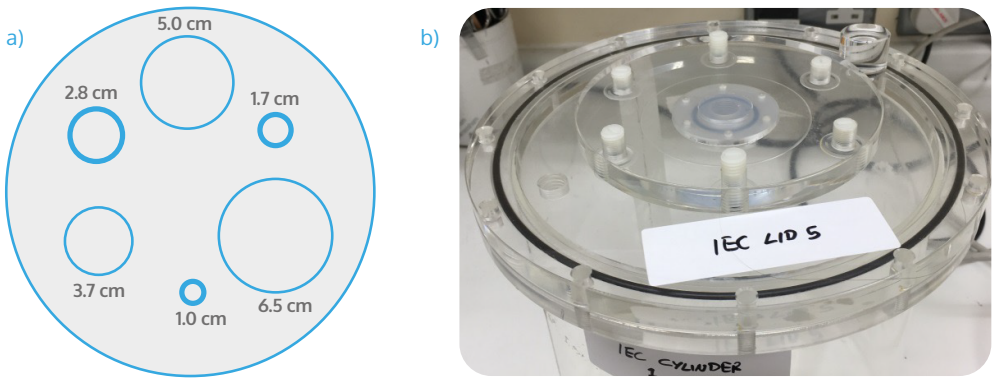

Figure 1
a) sphere positions within the IEC head phantom
b) modified IEC head phantom lid depicting filling holes for phantom background and spheres.

4. Fit the HEGP collimators to the camera.
5. Tape bench cote / inco pad securely to the camera couch.
6. Position the phantom on its side in the centre of the field of view ensuring the symmetry axis is coincident with the axis of rotation of the SPECT system. Mark the position of the phantom on the inco pad.
7. Acquire a SPECT/CT scan with the protocol detailed in Table 2 acquiring for 60 seconds per projection.
8. Remove phantom from scanner bed.
9. Fill the 3.7, 5.0 and 6.5 cm diameter spheres with the solution, avoiding air bubbles.
10. Return the phantom to the scanner bed and place in same position as for the previous acquisition.
11. Acquire a SPECT/CT scan with the protocol detailed in Table 2 with 60 s per projection.

Recovery Factor Creation

Procedure:

1. Reconstruct the images using the parameters listed in Table 3.
2. Define a spherical volume of interest (VOI) on the CT matching the dimensions of each sphere.
3. Calculate the mean counts per second for each sphere.
4. Divide this by the known activity concentration of the counts in each sphere, decay corrected to the acquisition time.
5. Plot these factors against the known volumes of the spheres, listed in Table 4.
6. Fit the following curve to the points:

$$RC_{fit} = \frac{\alpha}{1 + (\delta / x)^{\beta}}$$

Where x is the sphere volume, α, β and δ are the coefficients of fit.

In this way a recovery coefficient can be derived based on the CT defined volume of the lesion. These curves will be dependent on the method used to outline the lesions, the acquisition and reconstruction protocols. They may need further modification as the protocols are further optimised.

System Volume Sensitivity Measurement

The system volume sensitivity characterises the system's response to a uniform concentration of activity. The phantom will need to be stored at each site for at least five weeks following these measurements.

Prepare the Phantom

Equipment:

- 40 MBq liquid ^{131}I
- 1 g potassium iodine and 1 g sodium thiosulphate
- Hollow phantom with fillable volume greater than 6 l
- Radionuclide calibrator with factors for ^{131}I traceable to the national primary standard
- Approximately 90 minutes scan time

Procedure:

1. Determine the volume of the empty phantom by measuring the weight of water needed to completely fill it.
2. Add potassium iodine and sodium thiosulphate, agitate the solution, and secure lid.
3. Draw up 10 ml of background water from the phantom.
4. Draw up 40±2 MBq ^{131}I into syringe.
5. Assay syringe with appropriate calibration factor and note syringe activity and assay time.
6. Dispense contents of syringe into phantom. Redraw the solution within the phantom up into the syringe several times to wash the syringe contents into the phantom.
7. Measure and note the syringe activity with the cap on, this should be negligible.
8. Agitate the phantom to mix.
9. Remove any remaining air bubbles with the solution drawn from the phantom in step 1.

Sensitivity Factor Creation

Procedure:

1. Fit the HEGP collimators to the camera.
2. Tape bench cote / inco pad securely to the camera couch.
3. Position the phantom on its side in the centre of the field of view ensuring the symmetry axis is coincident with the axis of rotation of the SPECT system.
4. Perform a 100 kcount/projection SPECT scan utilising the settings in Table 2.
5. Note the scan start time and count rate.

6. Reconstruct the projections using the reconstruction parameters listed in Table 3.
7. Calculate the average counts per minute for the SPECT acquisition, A, by dividing the total counts imaged by the total elapsed time.
8. Calculate the source activity concentration (decay corrected activity in the phantom / phantom volume), B_c, at time T, halfway through the acquisition.
9. Calculate the system sensitivity factor as A/B_c.

Dead-Time Characterisation

Dead-time factors are to be used to correct the acquired image counts for counts lost due to detector paralysis. This procedure checks that the system correctly handles high activities of 131I and identifies artefacts that may occur at high count rates.
Before making this calibration all centres need to check with the manufacturers that their systems are set-up to acquire at high count rates of ^{131}I. This may be verified by acquiring a check image of the vial before commencing the following measurements.

Dead-Time Measurement

Equipment:

- 3700 MBq capsule of ^{131}I
- Scatter phantom

Procedure:

1. Assay the capsule with the calibration factor appropriate for ^{131}I capsules.
2. Fit the HEGP collimators to the camera.
3. Position the flat end of the phantom on the couch so that the top is level horizontally.
4. Ensure that the phantom is positioned in the centre of the detector field of view.
5. Position one detector level with and as close as possible to the phantom's upper flat surface and the other detector as close as possible to the underside of the couch.
6. Note:

Table height	_____
Table position	_____
Detector radius (1)	_____
(2)	_____

7. Acquire a 10 minute static planar scan with the energy window settings given in Table 2.
8. Position capsule in the scatter phantom and acquire a 100 kcount static planar scan with the energy window settings in Table 2.
9. Note the scan start time and count rate.
10. Repeat the background and capsule scan according to the scanning schedule listed in Table 5 recording the scan date, start time and count rate for each acquisition.

Table 5
SCANNING SCHEDULE FOR DEAD TIME MEASUREMENT USING DECAY METHOD

Nominal A(MBq)	Nominal day	Scan date & start time	Count rate (kcps)	
			Background	Capsule
3700	0			
3113	2			
2402	5			
2020	7			
1700	9			
1430	11			
1203	13			
1012	15			
716	19			
391	26			
196	34			
90	43			
58	48			
41	52			
21	60			

Dead-time Factor Creation

1. Check each image for artefacts and note the activity at which any begin to occur.
2. Determine the activity of the phantom at each time point, decay correcting for acquisition time.
3. Check the total peak window counts acquired at each time point and divide by the acquisition length to find the count rate at each activity for each detector, m.
4. Plot the count rate against phantom activity.
5. Linear fit the points up to 100 MBq and extrapolate to 3700 MBq, to show the expected true counts, n.
6. Calculate the correction factor at each activity level as n/m.
7. Correct each image using TEW correction and then check the corrected count rate in each image.
8. Plot these against activity and calculate the correction factors required for TEW correction.

^{131}I WB Planar Calibration Factor Measurement

The scans acquired in section Error! Reference source not found. can be utilised in the count-rate dependent calibration factors for planar scanning.

Procedure:

1. Calculate the average counts per minute, A, by dividing the total counts imaged in a ROI encompassing the majority of the counts by the total elapsed time.
2. Calculate the source activity, B, at time T, halfway through the acquisition.
3. Calculate the system sensitivity factor as A/B for each activity.
4. Plot system sensitivity factor against count rate.

References

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RECOMMENDATION 3.2

Optimisation of radiation protection of medical workers

MEDIRAD Scientific Goals and Research Results

The advice and figures of RP efficiency in the present recommendations are reported as (MC), (ST), (PH) depending whether they were produced using results from Monte Carlo simulations, staff measurements or phantom measurements, respectively. Where necessary, literature data (LI) were also used for completing the recommendations.

Caps

- PRO: potential for dose decrease to the brain in specific conditions

(MC) Results of MC simulations showed a dose reduction of 35% averaged over several configurations. (PH) Phantom measurements showed a considerably lower average reduction (7%), indicating the great influence of the irradiation conditions.

- PRO: protection comparable for lead and lead-free caps

(MC) Results of MC simulations showed comparable reduction of the brain dose, ranging from 10% to 43% depending on the configuration.

- PRO: more comfortable than the lead mask

In general, a lead cap is considerably lighter than a mask (e.g., 3 times lower weight for a lead cap) and does not impair vision. However, the protection level is lower than for the masks investigated.

- PRO / CON: efficiency strongly depends on staff position and head orientation

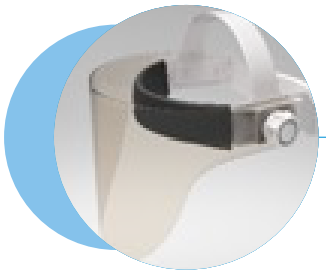
(MC) The closer the staff member is to the centre of the incident X-ray field, the smaller the dose reduction. Indeed, when the staff member is close to the beam, the backscattered X-rays can reach the brain through regions not covered by the cap. When the staff member is further away from the beam, a higher proportion of X-rays are intercepted by the cap. For instance, when the staff position was modelled at 40 cm from the field with the head perpendicular to the patient, the average reduction was only about 13%, whereas at 70 cm it was 37%. The height of the staff (and of the table) has logically an influence too.

- CON: dose reduction to the brain is not the attenuation characteristics of the device

(MC and PH) The lead equivalence of the cap and the resulting X-ray attenuation in a direct X-ray beam stated by the manufacturer are not representative of the dose reduction to the brain. Indeed, the scattered X-rays reaching the staff brain mostly come obliquely from below, through lower head regions not covered by the cap (LI: as much as 85% from MC simulations in a specific configuration [7]).

- CON: only limited parts of the brain are protected

(MC & PH) MC simulations and phantom measurements have shown that only some upper regions of the brain were protected. Dose reduction was lower for all regions when the physician was close to the primary beam; further away from the beam, protection of the hippocampus and the right side of the white matter was low whereas frontal and parietal lobes were more protected.



Masks

- PRO: potential for dose decrease to the eyes and brain

(MC) MC simulations indicated that the best mask model offered an average dose reduction of 53% and 62% to the eyes and the brain, respectively. (PH) Phantom measurements indicated dose reduction to the eye and the brain up to 10% and 17%, respectively. The mask was the most effective to protect the brain for left lateral projection which delivers the highest exposure to the physician when standing on the patients right hand side.

- PRO: More efficient than a lead cap for protecting the brain

(MC & PH) Both simulations and measurements showed that a mask was more efficient than a cap to protect the brain.

- PRO / CON: efficiency strongly affected by design

(MC) From three mask models investigated , the length of the mask and the lateral protections had a strong effect on the efficiency. Different designs could result in an additional 50% reduction in specific configurations. Long and enveloping masks offer better protection.

- PRO / CON: efficiency is strongly affected by staff position and head orientation

(MC) The staff distance from the X-ray beam entrance on the patient and the orientation of the staff head with respect to the beam could have a strong influence on the mask efficiency. For instance, the dose reduction to the brain and the left eye were very limited close to the beam (on average, 12.5% and 0.5%, respectively), further away from the beam, the reduction improved (on average, 43% and 4.1 %, respectively). (PH) The mask may not be effective in the frequently used PA projection in case it cannot be adjusted close enough to the physician's face.

- CON: heavier than lead-free cap

A mask can weigh about 400 g, while a lead-free cap can be three to four times lighter.

- CON: some parts of the brain are less protected than others

(MC & PH) Results from both simulations and measurements showed that the protection might be very heterogeneous and only limited regions, closer to the skull, might be protected. For instance, (MC) dose reduction for the left side of the white matter could be twice as much as for the right side. However, when no shielding was used, the right side was exposed to lower absolute doses than the left side.

[1]Two masks commercially available (VIS400 face mask (manufacturer unknown) and Full face style mask (Philips Safety products, USA)) and a third mask combining the characteristics of the previous masks.

Drapes

- PRO: significant dose decrease to hands, fingers and whole body dosimeter

(ST) Clinical measurements showed considerable dose reduction to the hand and fingers (20–40%) and to WB dosimeter (30–50%). (MC) Although MC simulations supported the decrease to the hands, no effect was observed on the WB dosimeter.

- PRO: no significant effect on patient dose

(MC) MC simulations have shown no significant effect on patient dose if the drape stays outside the primary beam.

- PRO /CON: influence of the positioning

(MC and PH) The drape efficiency increases when it is placed closer to the primary beam and when it covers the patient side closer to the cardiologist without gap at the level of the table. In addition, the drape protects better the organs in its direct vicinity such as the hands and the forearms.

- CON: limited effect on eyes and brain

(ST) Measurements on staff showed dose reduction up to 50% to eye lens; however, this was not observed in all participating hospitals, possibly indicating a strong influence of local practice. (MC and PH) Besides, MC simulations showed very limited dose reduction to eye lens and brain, between 0 to 13%.

- CON: risk to increase the dose if in the beam

(LI) If the drape is positioned partially in the primary beam, it will interfere with the automatic exposure system, which will increase the delivered dose.

Light lead and lead-free aprons

- PRO: protection comparable to that of conventional lead aprons for covered organs

(MC) For two models of lead-free and one model of lead apron, results of MC simulations showed comparable reduction of the effective dose E, ranging from 71% to 94%. (ST) From routine dosimetry measurements, no significant dose increase under the apron was observed for staff who changed a conventional lead apron for a light lead or a lead-free apron.

- PRO: potentially lower weight than conventional aprons

(LI) Lead aprons have been known to cause back pain [8]. Lead-free aprons can be lighter (up to 25% [9]).

- CON: Lead-equivalence claimed by manufacturers might not be met

(LI) Studies reported many cases of lead equivalence thicknesses being smaller than the values claimed by the manufacturers [10].

- CON: Dose enhancement for superficial organs with lead-free aprons

(LI) Dose enhancement reported in the literature for superficial organs (breast for instance) with lead-free apron [11] has to be further investigated in realistic clinical conditions as a possibly increased risk for cancer induction cannot be fully excluded.

Zero-Gravity suspended system (ZG)

- PRO: protection comparable to that of conventional lead aprons for covered organs

(PH & ST) For the regions normally covered by the lead apron, including the WB dosimeter, no meaningful difference could be observed during measurements. (MC) Simulations have shown a potential for dose reduction to organs normally covered by the lead apron.

- PRO: significant dose decrease to the eyes and brain

(ST) In clinical practice, 75% and 90% reduction to the eyes and the whole body dose were observed, respectively, when compared to ceiling suspended shield only. (MC) MC simulations delivered comparable reduction magnitude when comparing the device to a configuration with only a lead apron.

- PRO: lower weight on the operator than lead apron

(ST) Thanks to the suspending system, none of the weight of the ZG lies on the operator.

- CON: limited visibility of pedals

(ST) Due to the design of the ZG and its front lead glass, the operator cannot see the pedals of the X-ray system.

- CON: big investment

Compared to the price of conventional protective equipment, the price of the ZG is considerably higher and might not be accessible to all medical centres.

Ceiling-suspended screen

- PRO: potential for dose decrease to the eyes and the brain

(LI) The ceiling-suspended screen showed potential for significant dose reduction to the eye lens and the brain. Results of MC simulations indicated dose reduction to the eye closest to the beam (often the left eye) from 46% up to more than 92% [12], and reduction to the brain from 74% up to 94% [7]. Measurements on staff showed that the median eye dose was 40% lower for specific cardiac procedures but could be up to 90% lower for some radiology procedures [13].

- PRO: potential for dose decrease to the hands and the chest

(LI) A well-positioned screen can also protect the hands and the chest. Results of MC simulations showed dose reductions to the left hand by 21% to 68% [12].

- CON: efficiency strongly affected by screen position

(LI) The closer the ceiling-suspended screen is placed to the patient, the greater the efficiency. For instance, results of MC simulations showed that when the screen was positioned 15 cm above the patient the dose reduction to the white matter could be as low as 27%, while it was at least 74% when positioned 1 cm above the patient [7]. Flexible lead stripes attached to the bottom of the screen are therefore advised [12].

Lead glasses

- PRO: potential for dose decrease to the eyes

(LI) The lead glasses have a potential for significantly reducing the dose to the eyes, particularly to the eye closer to the X ray field (often the left eye). For instance, MC simulations of a wrap-around glass model lead to an average dose reduction as high as 74% to the left eye [14]. Phantom measurements showed similar potential with dose reductions up to 88% to the left eye [15].

- PRO: potential for dose decrease to the brain

(LI) The lead glasses can also offer limited protection to the brain. Results of MC simulations showed a dose reduction between 10% and 17% to the brain [7]. However, only few configurations were investigated, and the dose decrease is very dependent on the configuration and type of lead glasses.

- CON: efficiency strongly affected by design and operator position

(LI) MC simulations showed that glass design, in particular the shape and the air gap (distance between glasses and face), operator position with respect to the X ray beam and the head orientation have a significant effect on the efficiency. For instance, a factor two was calculated between the efficiency of two models simulated using MC software [14]. Phantom measurements confirmed these effects with the efficiency of five models tested in various conditions varying between 9% and 88% for the left eye and between 0% and 57% for the right eye [15].

- CON: dose decrease to eye-lens dosimeter is not representative of eye lens dose decrease

(LI) MC simulation [16] and phantom studies [17] have shown that a dedicated eye-lens dosimeter can severely under- or over-estimate the actual dose to the eye lens when lead glasses are worn. Ideally, an eye lens dosimeter should be positioned close to the eyes and under the glasses so that it would receive the same protection level as the eyes. However, this is rarely feasible in practice because the dosimeters are too big and/or uncomfortable to be put under the glasses.

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MEDIRAD

RECOMMENDATION 4

FUTURE RESEARCH ON MEDICAL RADIATION PROTECTION IN EUROPE

PROJECT TITLE

Implications of Medical Low Dose Radiation Exposure

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Introduction

Medical procedures are the largest source of exposure to man-made radiation in Europe. This medical use of radiation has greatly improved diagnosis and treatment, and is therefore justified by a net benefit to the patient. According to European legislation, radiation doses received by individual patients must be optimised in order to maximise the benefit/risk ratio to that patient. The past two decades have seen the competitive development of innovative medical technologies using ionising radiation which offer new diagnostic and therapeutic opportunities and require anticipation of potential risks. This is especially true for the diagnosis and treatment of cancer patients.

The ultimate goal is to optimise the use of ionising radiation for the diagnosis and treatment for each patient through an individualised approach based on generalised use of the most advanced risk-informed exposure protocols across Europe. However, significant differences in medical radiation exposure can be observed between different European countries, for similar protocols. Therefore, it is of great importance for the radiation protection community to conduct research, development, and innovation to further optimise and standardise the medical application of ionising radiation, and to disseminate best practice protocols throughout Europe, especially with respect to protecting patients from the adverse health effects of ionising radiation.

The MEDIRAD project has addressed specific areas of importance identified from clinical needs, with the aim of optimising radiation protection of patients and medical staff. While MEDIRAD Recommendations 1, 2, and 3 include further research needs specific to the technical fields covered by these recommendations, Recommendation 4 focuses on five key research issues which policymakers and relevant research communities are invited to consider.

The overarching perspective of the MEDIRAD project is to demonstrate the added value of close cooperation between medical and radiation sciences in addressing complex research questions. This set of key research issues does not seek to establish a new strategic research agenda, but rather highlight the strategic significance of addressing these five key research issues with adequate resources, and through the close cooperation of medical and radiation research communities.

1. Promoting optimisation in radiation therapy: deciphering the biological mechanisms of healthy tissue response, sensitivity, and adverse effects:

The growing number of cancer survivors in Europe, over half of whom are treated with radiation therapy, emphasises the priority to prevent or mitigate radiation-adverse treatment effects, which can have a significant impact on treatment outcome and on the patient's health and quality of life (QoL) [1]. Radiation effects in normal, healthy, tissue surrounding the tumour depends on many parameters, including the tissue type, dose/volume of the irradiation, functional status of organs at risk, age, smoking habits, comorbidities (diabetes, collagen vascular disease), and the patient's genotype [2]. Current understanding of the biological mechanisms underlying radiation adverse effects (cancer, fibrosis, non-cancer disease such as cardiovascular disease), combined with advanced methodological frameworks such as the adverse outcome pathway (AOP) approach, will facilitate research to identify and validate sets of molecular (genetic and epigenetic) biomarkers [3] of healthy tissue response, sensitivity, and adverse effects and of patient radiation susceptibility. These potential biomarkers could then be used to personalise treatments and support patient follow-up including treatment of adverse effects on healthy tissue when necessary.

2. Facilitating innovation in artificial intelligence (AI) for personalised diagnostic and therapeutic protocols:

Historically, diagnostic and therapeutic applications of ionising radiation have relied on consensual clinical protocols with standardised clinical dose and dose/volume recommendations. MEDIRAD stakeholders identified the development of more personalised diagnostic and therapeutic protocols as a need with significant impact on clinical practices. Given the large amounts of multisource patient data produced during routine clinical activities, AI and machine learning will play a major role in the use of big data for improving diagnostic and therapeutic applications of ionising radiation by helping to translate multisource data into clinical decision aids [4]. AI will help to develop diagnostic and treatment approaches that are better tailored to the specific characteristics of the patient and to improve therapeutic outcomes and minimise short and long-term adverse effects of radiation.

3. Modelling of radiation induced disease processes:

While the role of ionising radiation exposure in inducing DNA mutations is undisputed, research in the last decades has uncovered a multitude of other biological effects that contribute to the induction of cancer or other pathologies such as cardiovascular disease [5,6]. Key biological events in response to radiation exposure have been identified at different biological levels: from genes, RNA or proteins, to cells, tissues and organs, and they are interrelated. The challenge for future research is to develop models which correctly aggregate these biological effects to provide clinicians with advanced predictive tools.

The adverse outcome pathways (AOP) approach was designed by the OECD [7,8] to understand the complex health effects of toxic chemical compounds. European radiation and clinical research groups would benefit from the AOP investigation methodology by providing a common framework for scientific and clinical data integration. It would also open the way to future models that could take into account the effects of combined oncological treatments associating chemotherapy with radiation therapy.

4. Implementing EU-wide epidemiological studies to enhance quality and safety of medical radiation applications:

The use of ionising radiation in medicine represents a tremendous benefit for the diagnosis and treatment of diseases. While the benefits to the patient largely outweigh the risks, assessing the long-term adverse effects of radiation exposure is particularly important in cohorts of patients who may live for decades after exposure, particularly children [9]. Large scale clinical epidemiology studies, that follow exposed patients for decades, are essential to identify and quantify the late health effects of medical low, moderate, and high radiation doses and provide the basis for the implementation of high standards for quality and safety of medical radiation applications [10-12]. The success of such studies relies on careful patient follow-up and collection of detailed patient demographic, clinical, and dosimetric data, images and biological samples (through linkage with clinical, radiological, and therapeutic records) [3].

5. Optimising radiation-based medical imaging procedures for improved benefit/risk ratios and individualised procedures:

The use of ionising radiation in medicine may present some risk especially in situations that require repeated imaging for diagnostic, planning, or staging purposes and that result in non-negligible exposures, at least in certain body regions. Thus, there is a constant need for optimisation towards improved benefit/risk ratios and individualised procedures. Such optimisation will include the use of new methods and technologies, for better and more reliable diagnosis, the use of new evaluation techniques, such as those based on AI applications as described above, as well as the optimisation of existing procedures in terms of improved benefit/risk ratios on a population basis and for each individual patient. To achieve the latter, it is necessary to investigate the patient exposure in a more accurate and meaningful basis and correlate this information to the required image quality, which needs to be analysed and evaluated for each imaging procedure of each patient.

1

Promoting optimisation of radiation therapy: deciphering biological mechanism of healthy tissue response, sensitivity and adverse effects.

Overall recommendation

Conduct further research into adverse effects of ionising radiation on healthy tissues in order to contribute to the optimisation of radiation therapies.

» Specific recommendations:

1. Encourage research on healthy tissue radio-sensitivity and related biomarkers, based on adverse outcome pathways (AOPs) approaches.
2. Facilitate clinical transfer of predictive radio-sensitivity assays and related biomarkers for personalised treatment decisions.
3. Encourage research on early detection of radiation adverse outcomes and personalised patient follow-up.
4. Promote further clinical studies and optimise predictive assays of tissue response to ionising radiation.

1.1. Justification

Cancer is a major health concern in the European Union, with about 2.8 million new cases and 1.7 million deaths per year. It is indisputable that radiation oncology is a treatment strategy which plays a major role in the management of cancer patients. However, given the impact of acute and late normal tissue complications of radiotherapy on the patient's quality of life (QoL), efforts should be made to increase the efficacy of radiotherapy while decreasing side effects on healthy tissue.

Numerous normal tissue complication probability (NTCP) models have been developed. It is known that 5 to 10% of the patients will develop late adverse effects resulting from their radio-oncological treatment. The severity of radiation toxicity is the result of several biological parameters, including cell composition, cell renewal, and cell differentiation capacity, tissue organisation, as well as cellular radio-sensitivity [13,14]. The pathophysiology of exposed organs depends on many parameters, such as age, functional status of organs at risk, smoking habits, comorbidities (diabetes, collagen vascular disease) or patient genotype, and influence human response to ionising radiation [2]. Multiple genetic pathways such as DNA damage repair, oxidative stress, inflammation, and fibrogenesis contribute to the initiation and progression of adverse tissue reactions following radiation oncology treatment [15].

In addition, epigenetic factors may also play a crucial role in temporal and spatial control of gene activity. However, normal tissue responses to radiation remains to be fully explored and reliable biological markers are still not available to predict the onset and severity of radiotherapy side effects. The challenge today is to reduce a patient's adverse effects resulting from low, moderate, and high doses of exposure during medical interventions including radiotherapy as well as combined therapy, nuclear medicine, interventional radiology, and radiology. The ultimate aim is to promote early detection of cancer and non-cancer secondary effects. This early detection, especially in children, will help achieve better cancer post-treatment management and reduce the treatment constraints, improving thus patient's QoL [16,17].

1.2. Implementation

Four specific recommendations are presented hereinafter. Capturing the dose distribution in patients is a key first step for investigating healthy tissue response (occurrence and severity). However, a single patient can be subject to different radiation exposures during the diagnosis and the treatment of his/her tumour. For example, patients undergoing radiotherapy often receive radiation doses outside the target volume from a combination of diagnostic imaging, radiological treatment planning imaging, nuclear medicine treatment planning imaging (for example from a PET/CT study for radiotherapy treatment planning purposes), treatment verification imaging, as well as peripheral doses to the treated volume from the radiotherapy (external beam therapy or radionuclide therapy) treatment.

In that respect, dosimetrically combining different radiation exposures in an accurate way is a challenging task, and requires adapted methodology. Implementing and analysing patient dose repositories is a further technical challenge.

1.2.1. Encourage research on normal tissue radio-sensitivity and related biomarkers based on adverse outcome pathways (AOPs) approaches.

There is a crucial need to measure individual tissue response and predict individual risk of adverse effects after diagnostic and therapy procedures, as well as to identify subjects at greater risk of radiation-induced disease. To this end, the adverse outcome pathway (AOP) framework, which has not been fully explored in radiation research, would help guide relevant research on subsequent risk assessment in cancer and non-cancer diseases related to radiation exposure. AOP were experimentally implemented within MEDIRAD to model a path to cardiac toxicity as an adverse outcome, and to help identify relevant molecular and imaging biomarkers.

These, if validated, would be used in daily clinical practice for screening breast cancer patients, identifying those at risk of cardiovascular toxicity, and designing personalised follow-up after the completion of their cancer treatment. Large scale studies should be encouraged to identify the robustness of relevant biomarkers that can be translated to the clinic to detect early effects or identify patients for which personalised follow-up/screening and/or treatment approaches are required. In addition, radiation research has also been conducted for identifying relevant biomarkers of susceptibility to radiation-induced cancer, which could identify patients for whom alternative diagnostic and treatment approaches are needed.

Large scale epidemiological studies of patients need to integrate radiation-responsive genes, single nucleotide polymorphism (SNP) discovery through genome-wide association studies (GWAS), epigenetics, and next-generation sequencing, to obtain a holistic view of adverse effects of radiation oncology treatment and identify AOP for individual adverse effects and key related biomarkers.

» Target audience: medical professional organisations, scientific communities.

1.2.2. Facilitate clinical transfer of predictive radio-sensitivity assays for personalised treatment decisions.

There is a growing tendency to move towards 4P Medicine (Predictive, Preventive, Personalised, Participatory), with a specific focus in MEDIRAD project on predictive and personalised medicine. Over the last decades, a large number of tests for evaluating radio-sensitivity have been investigated, of which only SNP assays and the radiation-induced lymphocyte apoptosis assay (RILA) [18] have shown replicated performance in the development phase. Several genes involved in tissue response to radiation were identified because homozygous mutations resulted in unusually severe reactions to radiation-oncology treatment (angiotensinogen, ataxia telangiectasia-mutated, etc.) [19,20].

Development of predictive radio-sensitivity assays and molecular biomarkers should focus on their use in daily clinical decision making (treatment, follow-up, interventions). In this sense, developing methodologies that can be implemented into clinical practice should be addressed. This research will require large clinical studies to identify normal tissue-specific and significant molecular modifications as a valid signature for radiation sensitivity or healthy tissue response [21]. Advanced bioinformatics and mathematical modelling are crucially needed to combine multiomics data for identifying robust and reliable predictive signatures that allow clinicians to identify patients most at risk.

» Target audience: medical professional organisations, medical practitioners, scientific communities.

1.2.3. Encourage research on early detection of radiation adverse outcomes and personalised patient follow-up.

Early detection of secondary and long term cancer and non-cancer diseases in cancer survivor patients would improve cancer management, patient long term QoL, and provide cost-effective therapeutic interventions to reduce the side effects of radiation oncology. MEDIRAD research reinforces that secondary complications after radiotherapy can be substantial. For example, cardiovascular toxicity can develop after radiotherapy of thoracic cancer (breast cancer or lung cancer), and repetitive low doses from CT-scanning can lead to leukaemia and brain tumours. Costs associated with adverse outcomes following radiation oncology are often hard to quantify, because they represent a small part of a complex disease management protocol. Personalised risk-adapted approaches should decrease the rate of late toxicities by providing more effective treatments and lower long-term costs of cancer survivorship, thereby improving the patient's QoL.

The use of predictive assays (including molecular and imaging biomarkers) described above will help to anticipate clinical outcomes. Careful long-term clinical follow-up studies should focus on patient groups at particularly high risk of radiation-induced adverse effects (cancer and cardiovascular toxicity) due to their age, genetic predisposition, and comorbidities. Strategies to mitigate side effects should be also encouraged in combination with early screenings.

» Target audience: policy makers, European research communities (Euratom & Horizon Europe Health), scientific communities, patient associations, health authorities.

1.2.4. Promote further clinical studies and optimise predictive assays of tissue response to ionising radiation.

Research has been performed in MEDIRAD to identify predictive assays for cardiac tissue response to ionising radiation. A predictive signature of cardiotoxicity was proposed as a specific combination of molecular markers (MEDIRAD cardio signature). However, both the prevalence and severity of adverse effects vary from patient to patient, as can be expected from the ethnic, geographic, gender, and age diversity of the general European population.

Inevitably, the conditions under which a biomarker is applied will differ in some ways from those under which it was developed.

Thus, predictive assays, including multiple biomarkers, need to be tested and validated [3] in diverse cohorts of patient and medical settings to ensure their clinical robustness. Moreover, optimising methods to test predictive assays in easily accessible body fluids such as urine and saliva would facilitate their clinical implementation in daily practices, in a cost-effective way, to monitor patient for both risks and benefits of radiation-based diagnosis and treatment protocols. All this requires large scale clinical studies with adapted procedures for easy access to clinical data, biobanks, and patient samples (body fluids and tissue samples). This will be essential for validating and optimising assays that can be translated to the clinic to detect early effects, or identify patients for which personalised follow-up/screening and/or treatment approaches are needed.

» Target audience: policy and clinical decision makers, European research communities (Euratom & Horizon Europe Health), scientific communities.

1.3. MEDIRAD scientific achievements supporting these recommendations

- MEDIRAD identifies potential biological indicators of dose (H2AX in blood PBMC) to assess the impact of low dose radiation exposure from 131I-NaI radioiodine ablation of thyroid cancer in nuclear medicine.

- MEDIRAD brings the proof of concept for early detection of innovative circulating biomarkers (microparticles and specific microRNA) for radiation-induced cardiotoxicity in preclinical studies.

- MEDIRAD brings the proof of concept for early detection of innovative circulating biomarkers (microparticles, specific microRNA, and specific DNA methylation) of radiation-induced cardiovascular toxicity from breast cancer radiotherapy in clinical studies.

- MEDIRAD identifies the potential miRNA candidates as biomarker of radiation sensitivity of paediatric CT patients.

2

Facilitating innovation in artificial intelligence (AI) for personalised diagnostic and therapeutic protocols.

Overall recommendation

Promote EU-wide research strategy to use AI for optimising radiation protection in radiation oncology.

» **Specific recommendations:**

1. Promote a "dosiomic" approach based on optimised patient-specific 3D distribution of radiotherapy dose.
2. Promote development of "radiomics" supporting personalised medicine.

2.1. Justification

The last two decades have seen the development of innovative medical technologies using ionising radiation and offering new diagnostic and treatment opportunities. Optimisation of radiation protection for patients highlight the need for prospective research on these new or optimised procedures for medical imaging, nuclear medicine, as well as radiation therapy.
A special focus should be made on (diagnostic and therapy) quality assessment, dose assessment, new promising approaches for imaging, and/or therapeutic applications (new radiopharmaceuticals, emerging technologies, and techniques in radiation therapy and imaging, hypo-fractionation therapy, flash or micro-beam therapies, new geometries or detectors for imaging, etc.).

Within the MEDIRAD project, different strategies were tested with the objective of re-enforcing image, dosimetry, and biology-based risk assessment for new diagnostic and therapeutic applications of ionising radiation. Substantial progress was made in the development of (i) a 3D spatial features for dose distribution (OpenDose3D) in nuclear medicine, (ii) a semi-automatic evaluation of physics-based image quality for chest CT, (iii) a model of patient dosimetry at the voxel scale, and (iv) an automatic segmentation tool to delineate heart sub-structure. This work illustrates the potential benefits, and the complexity of, implementing computational analysis of patient dosimetry (dosiomics) and patient imaging (radiomics).

These developments are based on qualitative and quantitative performance analyses with high throughput extraction of numeric radiologic, dosimetric, and biological data to obtain predictive or prognostic information, thereby increasing diagnostic and treatment efficacy and limiting as much as possible adverse effects of ionising radiation. Artificial intelligence (AI) technology can be used to support these development.

2.2. Implementation

2.2.1. Promote dosiomic approaches based on optimised patient-specific volumetric distributions of dose imparted.

Dosiomics was initially introduced as a novel texture analysis procedure to harvest dose features that encode the spatial, temporal, and statistical distribution of radiotherapy dose [22]. In this regard, MEDIRAD's results highlight the importance of developing computational methods for volumetric distribution calculations based on patient-specific characteristics for all medical procedures using ionising radiation (including for example: CT, interventional, nuclear medicine, and radiotherapy procedures) taking into account different dose indicators for different types of procedures to get comparable, and meaningful, information on normal and pathological tissue doses between individuals.

Moreover, MEDIRAD results provide a proof of concept for developing optimal dose measurement protocols in nuclear medicine for the accurate estimation of normal tissue absorbed doses (mean organ doses and 3D distributions) using validated quantitative imaging and dose/volume calculation methods. Refinement, validation, and implementation of new bio-kinetic models are needed for dosimetry in molecular radiotherapy using for example physiologically-based pharmacokinetic (PBPK) models for the individual assessment of bio-kinetics.

Finally, dosiomics are increasingly used in clinical studies aimed at improving the prediction of clinical outcomes (including tumour control probability (TCP) and normal tissue complication probability (NTCP) models) in radiation oncology.

The use of dosiomics in clinical practice could represent a powerful tool to better handle the three-dimensional (3D) dose spatial, temporal and statistical information if compared with conventional tools, such as dose-volume histograms [23].

Automatic delineation algorithms have demonstrated their efficacy compared to previous methodologies (e.g. atlas, thresholding, etc.). AI (Deep Learning) could play a role in the prediction of the delivered dose according to the patient's anatomy, with the advantage of a short calculation time compared to treatment planning systems (TPS).

» Target audience: medical professional organisations, medical physicists, radiation oncologists, medical practitioners, scientific communities, European research communities (Euratom & Horizon Europe Health).

2.2.2. Promote development of radiomics supporting personalised medicine.

AI is leading to a significant evolution of automatic diagnosis systems supporting researchers and clinicians. Radiomics provides high-performance qualitative and quantitative analysis, consisting of high-throughput extraction of digital medical imaging data of the tumour and the surrounding organ at risk, to obtain predictive and/or prognostic information (treatment efficacy and toxicity) of individual patients undergoing radiotherapy treatment [24,25]. MEDIRAD contributed to highlighting the importance of developing computational methods for the diagnosis and prognosis of image and functionality-based assessments of cardiac toxicity.

Radiomics need to be further implemented to develop optimisation approaches, for target and non-target tissue, on an individual patient basis. Investigation on 1) variations in tumour heterogeneity and surrounding healthy tissue response during radiotherapy treatment and 2) definition of the minimal spatial and temporal variations that could have an impact on dose distribution to the target volume and the organs at risk should be encouraged, as they will contribute to the optimisation of personalised clinical protocols.

Such approaches would need to focus on specific applications / diseases before being transferred to the clinical environment in daily practices, with the aim of facilitating, and not superseding, clinical interpretation of patient's data.

» Target audience: medical professional organisations, medical practitioners, European research communities (Euratom & Horizon Europe Health), scientific communities.

2.3. MEDIRAD scientific achievements supporting these recommendations

- MEDIRAD has developed and validated a prediction model to assess the risk of acute coronary events (ACE) in the first 10 years after radiotherapy in individual breast cancer patients based on 3D cardiac dose distribution and need for further dosiomic approach.

- MEDIRAD brings the proof of concept for developing optimal dose measurement protocols in nuclear medicine for the accurate estimation of normal tissue absorbed doses (mean organ doses and 3D distributions) using validated quantitative imaging and dose/volume calculation methods.

- MEDIRAD refines, validates, and implements a new bio-kinetic models are needed for dosimetry in molecular radiotherapy using for example physiologically-based pharmacokinetic (PBPK) models for the individual assessment of bio-kinetics.

- MEDIRAD identifies potential specific image markers from echocardiography, cardiac CT, cardiac MRI, and circulating molecular biomarkers for early detection of cardiac changes arising within the first 2 years after breast cancer radiotherapy.

- MEDIRAD identifies the potential miRNA candidates as biomarker of radiation sensitivity of paediatric CT patients.

3

Modelling of radiation-induced disease processes.

Overall recommendation

Develop biologically based models that integrate biological processes of radiation toxicity and relate them to radiation-induced disease risk.

» **Specific recommendations:**

1. Conduct further research on radiation effects on existing cardiovascular disease.
2. Support integrative analyses taking into account effects at several levels of biological organisation.
3. Support efforts to develop radiation-related adverse outcome pathway (AOP) approaches.

3.1. Justification

Standard radiation epidemiological models can be usefully complemented by the development and use of so-called "mechanistic" or "biologically-based" models aiming to relate disease risk to underlying disease processes [26] as epidemiological studies alone are insufficiently powered to directly determine risks at low doses. Biologically based models therefore allow improving risk assessments by taking into account known or postulated low dose mechanisms in the process of extrapolating risk from high to low doses [27].

Understanding underlying processes may, in addition, help identify subgroups of patients with increased risk, based on interactions with other risk factors, or pre-existing conditions. Over the last years, knowledge of disease aetiology has greatly improved, and more realistic and predictive models have been developed [28]. The OECD has promoted the concept and development of adverse outcome pathways (AOPs) to facilitate the inference of causality and the transfer of results from different chemicals or other stressors [29,30].

AOPs are a framework to provide a science-based but simple scheme of successive biological processes that link the perturbation of a specific biological target to a disease or other adverse outcome. At present, AOPs are used only to provide rationale for the existence of risk but not for assessment of its magnitude. Although first attempts have been made, the concept has not yet widely been adopted in radiation research and radiation protection. The development of an AOP related to radiation-induced cardiovascular diseases has been initiated in a recent workshop [31].

Biologically based models can relate the accumulated knowledge of AOPs to radiation-induced cancer risk. State-of-the art normal tissue complication probability (NTCP) models in radiation oncology describe probability and severity of normal tissue complications as a function of dose distribution in the heart volume and its surrounding cardiovascular structures.

Biologically based models provide interfaces for stressors acting on different levels of biological organisation from gene to tissue. In future applications, models could be informed by cardiovascular disease-related stressor-agnostic AOPs to investigate the toxicity coming from combined (radio-chemo-immuno) therapy [32].

3.2. Implementation

3.2.1. Conduct further research into radiation effects on existing cardiovascular disease.

Radiation can injure different heart structures including the pericardium, the myocardium, the heart valves, coronary arteries, or the heart's electrical system, depending on the dose distribution to specific heart sub-structures. Related cardiac radiation pathologies include pericarditis, premature coronary artery disease, atherosclerosis, myocarditis, or congestive heart failure [33]. A detailed risk analysis revealed atherosclerosis as the most important underlying disease for acute cardiovascular events following radiotherapy for breast cancer patients [34].

Hence, modelling risk of acute cardiovascular effects related to atherosclerosis has been one of the focuses of the MEDIRAD work programme. This involves not only studying the effects of ionising radiation on the early phase of cardiovascular disease, but conducting experiments and developing biologically based models of the effect of radiation at later stages, on already established disease. Radiopathologists and mathematicians should be encouraged to work together in order to develop new models of risk for other radiation induced cardiac diseases (congestive heart failure and pericarditis, among others).

» Target audience: medical professional organisations, medical practitioners, European research communities (Euratom & Horizon Europe Health), scientific communities.

3.2.2. Support integrative analyses taking into account effects at several levels of biological organisation.

To fully exploit data obtained from several biological levels, an integrative analysis is necessary. It can help to better understand and quantify the relations between different levels and higher confidence can be achieved through a more comprehensive picture of disease processes. Network analysis can cope with the large amount of data obtained from modern omics technology. Therefore, the integration of information at several levels by network analysis should be considered and supported in the research of disease pathways.

» Target audience: policy makers, research community.

3.2.3. Support efforts to develop radiation-related AOP approaches.

A major motivation for developing the concept of AOPs was facilitating regulatory decision-making by aggregating knowledge in an accessible format. These pathways are a practical tool to assess the evidence and identify knowledge gaps, highly relevant for researchers as well as funding agencies, as this approach facilitates the integration of results from complementary research projects. Thus, development of radiation-related AOPs should be encouraged.

Particular effort should be made to reduce barriers between disciplines and provide more support to mathematics, statistics or informatics in medical research project for disease modelling, thus favouring a quantitative risk estimate and not only a rationale for risk existence. Biologically based models help assessing the contribution of different pathways to risk.

» Target audience: policy makers, regulatory authorities, European research communities (Euratom & Horizon Europe Health), research community.

3.3. MEDIRAD scientific achievements supporting these recommendations

- MEDIRAD has developed a biologically based risk model suggesting radiation effect complicated lesions (plaques).
- MEDIRAD has developed a biologically based risk model suggesting that heart sparing techniques in radiation therapy is needed also for older patient.
- MEDIRAD has developed a network analysis that links biomarkers on different levels of biological organisation (molecular and cardiac tissue).
- MEDIRAD has developed a biologically based model informed by network analysis allowing quantitative risk assessment of cardiotoxicity within the AOP concept.

4

Implementing EU-wide epidemiological studies to enhance quality and safety of medical radiation applications.

Overall recommendation

Conduct large scale clinical epidemiological follow-up of patients to understand and quantify late health effects of radiation and provide evidence for setting high quality and safety standards for medical radiation applications.

» **Specific recommendations:**

1. Foster interactions between clinicians, radiobiologists, physicists, and epidemiologists to provide a clinical epidemiological framework for patient follow-up.
2. Provide funding through concerted provisions in Horizon Europe (Health) and Euratom (Radiation Protection) research programmes.
3. Conduct patient follow-up after medical ionising radiation exposure by means of well-designed clinical epidemiological studies, focusing on most at risk populations.
4. Promote reliance on, and maintenance of, appropriate patient registries and secure mechanisms for linking data across registries for patient follow-up and dose optimisation, respecting patient privacy.
5. Consider patient-specific dose modifiers in derivation of dose estimates as appropriate to different settings.
6. Increase capability for radiation dose tracking and managing programmes to provide relevant and standardised dose estimates.
7. Validate biomarkers of radiation exposure, effects and sensitivity to better identify patients at higher risk of radiation-induced health effects.
8. Use results of clinical epidemiological studies to optimise treatment and imaging protocols and patient follow-up.
9. Harmonise data protection guidelines at the European level to facilitate EU-wide epidemiological studies in medical radiation protection.

4.1. Justification

Historically, the optimisation of radiation-based diagnostic and therapeutic protocols has been pursued through the analysis of the benefit/risks balance for the patients, informed, for diagnostic radiation, by existing low dose risk estimates from epidemiological studies of higher dose populations (e.g. the atomic bomb survivors) and, for radiotherapy, by the clinical follow-up of patients for up to 5 years after the end of the treatment, a medical consensus period during which the success of the therapy, and the occurrence of adverse effects of radiation exposure could be appropriately assessed.

To this day, numerous clinical trials are being conducted to support the ongoing optimisation of new technologies or new therapeutic protocols in radiation oncology. Typical clinical outputs of such trials include the occurrence and the severity (CTCAe grading) of the adverse effects correlated to dose/volume (dose-volume histograms), and imaging data that allow evaluation of normal tissue complication probability (NTCP). These trials do not, however, allow the evaluation of longer-term effects (on cancer and non-cancer endpoints, including QoL) in the growing number of cancer survivors in Europe. Therefore, careful long-term clinical epidemiological follow-up of these patients is needed.

Moreover, outside of clinical trials, observations based on patient follow-up are often difficult to interpret because subjects included may not be representative of the relevant patient population and/or because key information on other risk factors or effect modifiers is not available.
The current recommendation therefore focuses on promoting the general use of a "clinical epidemiology" framework for patient follow-up whereby all appropriate disciplines collaborate (clinicians, biologists, dosimetrists, and epidemiologists). This includes:

- Ensuring the EU patient registries include all the necessary information for the patient follow-up and for dose optimisation in a standardised fashion.
- Ensuring the EU patient registries can be linked.
- Tracking and managing radiation exposure and dose information.
- Taking into account patient-specific characteristics to derive doses;
- Validating, developing and implementing relevant biomarkers (example.g. imaging biomarkers in the follow-up of CVD in breast cancer patients) of exposure, susceptibility and early effect in the clinical epidemiological follow-up.

Such a framework will be useful to ensure follow-up data can be used to draw appropriate conclusions regarding radiation effects, and improve treatment and diagnostic protocols. The collaboration between epidemiologists and clinicians is an added value.

Clinical epidemiological investigations (i.e. the clinical follow-up of patients exposed to medical sources of radiation using epidemiological methods) require the follow-up of large exposed populations for decades to i) identify and quantify the late effects of medical low, moderate and high radiation doses on the health and wellbeing of patients; ii) provide the evidence base for

the development and implementation of high standards for quality and safety of medical radiation applications; and iii) provide a mechanism for continuous surveillance of the effects of the medical radiation exposure. The success of optimising patient follow-up is determined by efficient patient monitoring and quality of demographic and clinical data repositories linked with appropriate dose data and imaging repositories.

In the years to come, there are strategic opportunities in continuing to leverage on cohorts of patients treated with radiotherapy (including both novel and traditional modalities), patients at higher risk of radiation-induced health effects (for example cohorts of ataxia telangiectasia heterozygotes), and cohorts with relevant "higher-dose" diagnostic exposures (including in nuclear medicine), bringing together data related to (i) patient dose information (including patient dose-volume histograms), (ii) relevant outcomes (including toxicity and clinical indicators), and, where relevant (iii) information on factors that may affect sensitivity (genetic and epigenetic factors, other exposures, other patient characteristics).

Long-term patient follow-up should be ensured to adequately assess the short, medium and long-term effects of the exposures. This clinical epidemiological framework approach requires strong cooperation between clinicians and radiation protection research communities, including epidemiologists, biologist, physicists, and dosimetrists in developing adequate follow-up protocols and identifying important clinical questions to be studied. It will also require high quality achievements in patient monitoring methodologies, and in the quality of patient demographic and clinical repositories, linked with dose data, molecular bio-indicators information, and imaging repositories through innovative AI applications which allow the processing of vast number of data sets.

4.2. Implementation

4.2.1. Foster interactions between clinicians, radiobiologists, physicists, and epidemiologists.

Such interactions, generating a close collaboration between oncologists and other clinicians, researchers and medical professionals from relevant disciplines including epidemiology, medical physics, radiobiology, and radiation protection, would enable the development of a standard clinical epidemiological framework for the follow-up of patients exposed to radiation in medicine, the identification of clinical research priorities and the design, operational planning and implementation of future Europe-wide clinical epidemiology studies.

» Target audience: European research communities (Euratom & Horizon Europe Health), medical professional organisations, scientific communities.

4.2.2. Provide funding through concerted provisions in Horizon Europe (Health) and Euratom (radiation protection) research programs.

The conjunction of programme objectives from the Horizon Health and Euratom research communities in Europe would offer unique opportunities to facilitate the development of large scale trans-European clinical epidemiological studies in medical radiation protection, scientifically and clinically design to be fundable.

» Target audience: European research communities (Euratom & Horizon Europe Health).

4.2.3. Conduct patient follow-up after medical ionising radiation exposure by means of well-designed clinical epidemiological studies, focusing on most at risk populations.

Apart from the use of a more standardised clinical epidemiological framework of long-term patient follow-up, which would help ensure that patient cohorts are "portable" over time through successive research consortia, specific studies should be set-up to answer most pressing clinical and radiation protection needs. These studies should help assess the risk of late health effects of radiation exposure on patient health and well-being, and provide the evidence base for optimising patient care protocols.

A single large-scale epidemiological study cannot answer all questions. Hence specific Europe-wide large-scale studies should be conducted in different priority populations. Of particular importance at present are:

- Cancer patients undergoing radiation oncology, in particular paediatric patients and patients receiving new radiotherapy modalities [35,36].
- Cancer patients undergoing nuclear medicine procedures for diagnostic and treatment purposes [37].
- Patients at particularly high risk – in particular paediatric populations and patients with specific genetic profiles (none exclusively BRCA1/2 mutation carriers, AT heterozygotes) which may confer a higher risk of radiation-induced health effects and may warrant alternative treatment/diagnostic strategies.
- Patients treated through interventional radiology [38,39].
- Large populations undergoing recurrent CT scanning and other radiological imaging and screening procedures [40- 42].

As AI innovative developments are expected to make a major contribution to the future optimisation of the patient follow-up, consideration should be given to embed AI applications in the design of future European clinical-epidemiology studies, facilitating the exploitation of large repositories related to patient dose/image/biology data sets.

» Target audience: medical professional organisations, European research communities (Euratom & Horizon Europe Health), scientific communities.

4.2.4. Maintain appropriate Europe-wide patient registries and secure mechanisms for linking data across registries while respecting patient privacy.

Clinical epidemiological studies need to rely on well-designed and complete data registries. Interoperability between registries is essential in order to link all needed data on patient condition, treatment, outcomes, doses, and risk factors. However, for protecting patient privacy, it is essential that all registries be secure and that linking them is only feasible under the strictest security and privacy conditions and following the GDPR.

» Target audience: health authorities, medical professional organisations, scientific communities.

4.2.5. Consider patient-specific dose modifiers in derivation of dose estimates as appropriate to different settings.

This recommendation covers both diagnostic and therapeutic procedures. Absorbed dose to a specific organ, tissue or relevant volume varies from patient to patient, in particular in nuclear medicine, but also for external irradiation, depending, for example, on anthropomorphic parameters of the patient, something which is often not taken into account, particularly in diagnostic procedures.

» Target audience: medical professional organisations, scientific communities.

4.2.6. Increase capability for radiation dose tracking and managing programmes.

This will allow provision of relevant and standardised dose estimates for input both to clinical decision and epidemiological studies. Patients may receive radiation doses in many settings and up to now it is extremely difficult to collect all information in a comprehensive and standardised fashion.

» Target audience: medical professional organisations, scientific communities.

4.2.7. Validate biomarkers of radiation exposure, effects, sensitivity and susceptibility to better identify patients at higher risk of radiation-induced health effects.

Use of appropriate, sensitive, specific, and validated biomarkers of healthy tissue radiation response, radiation sensitivity and radiation susceptibility would greatly enhance the power of clinical epidemiology to assess health effects of radiation exposure and to identifying, in the clinic, subjects at higher risk of radiation induced health effects, and subjects with markers of early effect (for example imaging biomarkers for cardiovascular effects) for whom screening and/or alternative treatments or procedures may be adapted.

For this, collection, processing, and storage of appropriate biological samples is needed for the study of biomarkers (those currently available, as well as markers which may be developed in the future), together with patient's informed consent to the use of the samples for this purpose.

» Target audience: medical professional organisations, scientific communities.

4.2.8. Use results of clinical epidemiological studies to optimise treatment and imaging protocols and patient follow-up.

Rapid communication of results of clinical epidemiological studies is needed to ensure optimisation of protection and follow-up. This includes, for example, the follow-up of imaging biomarkers in women treated with radiotherapy for breast cancer, in order to screen for possible toxicity of radiation on the cardiovascular system, as observed in MEDIRAD.

» Target audience: health authorities, medical professional organisations, scientific communities.

4.2.9. Harmonise data protection guidelines at the European level to facilitate EU-wide epidemiological studies in medical radiation protection (see RECO 1).

Application of data protection and security recommendations, including the implementation of the GDPR, vary between member states and within, making it difficult to conduct large scale multinational clinical epidemiological studies in medical radiation protection. Guidance and harmonisation of practices are needed (see Recommendation 1) in order to ensure the feasibility of conducting informative clinical epidemiological studies of patients exposed to radiation, while ensuring privacy and security of their personal information.

Such studies are important as they provide a surveillance tool for monitoring the health effects of medical radiation exposure (including new treatment modalities) with implications for clinical management of patients and for dose optimisation.

Bringing together the Horizon-Europe Health and Euratom research communities would offer unique opportunities for the development of large scale trans-European clinical studies in medical radiation protection. The convergence of these two communities is key for preparing future clinical epidemiology studies. These studies should be planned and conducted as a close collaboration between clinicians, scientists, and medical professionals from relevant disciplines, including epidemiologists, medical physicists, radiobiologists, and radiation protection experts.

» Target audience: health authorities, medical professional organisations, scientific communities.

4.3. MEDIRAD scientific achievements supporting these recommendations

- MEDIRAD has implemented a retrospective cohort study (BRACE study): our two preliminary conclusions underpin (i) the heart is an important organ-at-risk in breast cancer radiotherapy and should be spared as much as possible (ALARA-principle) and (ii) multivariable NTCP-models provide information on the excess risk of acute coronary events on an individual patient basis, and can be used to decide if more advanced radiation technologies are indicated.

- MEDIRAD has implemented a multicentric prospective cohort study (EARLY HEART): our first results showed a dose-response relationship between subclinical left ventricular dysfunction (defined by a decrease in left ventricular global longitudinal strain 6 months after radiotherapy) and whole heart and left ventricular doses.

- MEDIRAD has set up of the nested case-control study of cancer risk in the cohort of CT patients involved collaboration between oncologists, radiologists, epidemiologists, dosimetrists, and radiobiologists. Update of EPI-CT cohorts of paediatric CT patients.

- MEDIRAD has implemented a nested case-control study of brain and haematological malignancies

- MEDIRAD has developed a biologically based model informed by network analysis allowing quantitative risk assessment of cardiotoxicity within the AOP concept.

5

Optimising radiation based medical imaging procedures in terms of improved benefit/risk ratios and individualised procedures.

Overall recommendation

Investigate new and optimise existing medical imaging procedures to improve benefit/risk ratios and personalised approaches.

» **Specific recommendations:**

1. Establish research on individualised benefit/risk ratio determination for diagnostic applications of ionising radiation.
2. Facilitate the broader implementation of detailed exposure characterisation for imaging procedures.
3. Conduct research determining indication dependent appropriate image quality.
4. Promote implementation of combined exposure and appropriate image quality determination for optimising benefit/risk ratios in existing and new diagnostic.

5.1. Justification

Today, the majority of patients arriving to a European hospital undergo one or more imaging procedures for diagnosis, treatment, or staging. Many of these procedures are based on the use of ionising radiation. Thus, for the average European population, medical imaging based on ionising radiation is one of the largest contributors (in some countries the largest) to the average

exposure of the population. Various procedures like CT, some interventional procedures, as well as some nuclear medical imaging procedures, represent potentially relevant exposures, particularly when they are repeatedly performed within the disease management process. Taking into account potential differences in the patient's response to radiation, the type of exposure, and the technology used, it is of great importance to define the patient-specific benefit/risk ratios for such procedures and optimise them in various scenarios.

These may include new technologies for individualised diagnostic approaches, optimisation schemes based on correlated analysis of suitable exposure parameters as well as image quality determination adapted for specific medical indication. Finally, it is relevant to transfer the optimisation into clinical practice, which requires a lot of research on how to implement the developed optimisation tools as well as to define appropriate image quality for the relevant indications.

When preparing the MEDIRAD project, the importance of optimising imaging procedures in terms of characterising and potentially improving benefit/risk ratios was already clear. Therefore, methods for exposure determination in various imaging procedures like chest CT, nuclear medical imaging, and some interventional imaging procedures had been developed, together with methods of subjective and objective image quality determination in chest CT. The example of chest CT, showed the importance of indication-based optimisation, especially with respect to image quality aspects, as well as the potential for correlated optimisation of image quality and patient specific exposure. It also proved that, by developing semi-automated tools, its implementation into clinical daily routine is feasible. However, this was only developed for unenhanced chest CT.

5.2. Justification

Based on the above four specific recommendations are presented. First of all, it is relevant to define how benefit/risk ratios can be determined for an individual patient. An individual patient can be subject to different radiation exposures depending on the patient specific status, individual sensitivity, and technology used. A combination of diagnostic imaging, radiological treatment planning imaging, nuclear medicine treatment planning imaging (for example from a PET/CT study for radiotherapy treatment planning purposes), treatment verification imaging, and imaging in staging purposes will determine the total exposure of the patient.

The second recommendation is thus to develop methods for patient-specific exposure characterisation at the organ level, shown for some examples in MEDIRAD for all relevant imaging procedures. This must be accompanied by research on indication dependent appropriate image quality and the corresponding methods to determine related characteristics. Finally, translating these results into optimisation schemes in daily clinical routine is a challenge that needs to be addressed.

5.2.1. Establish research on individualised benefit/risk ratio determination for diagnostic applications of ionising radiation.

As stated in the first overall recommendation, the adverse outcome pathway (AOP) framework has not been fully explored in the radiation field to guide relevant research on risk assessment of subsequent cancer and non-cancer diseases related to medical radiation exposure. However, once factors influencing the sensitivity and susceptibility of patients undergoing radiation exposure for diagnostic purposes are identified, this information has to be implemented for determining individualised benefit/risk ratios. In addition, it is necessary to understand how to deal with unknown potential risk factors.

MEDIRAD had identified potential influencing factors and has also determined exposure characteristics for individual patients undergoing chest CT imaging. Results clearly show that there various factors influence exposure at the organ level, including difference in local hospital practice, technological differences in the various hospitals, and patient parameters. In addition, using the example of unenhanced chest CT imaging, MEDIRAD showed that appropriate image quality is indication dependent. Therefore, it needs to be discussed how potential risk factors of individual patients, patient parameters, technology of imaging equipment, differences in local hospital practice as well as necessary diagnostic image quality and or potential diagnostic substitute procedures can be incorporated into benefit/risk ratio determination on an individual patient basis and if and for which procedures this would be necessary.

» Target audience: medical professional organisations, scientific communities for radiation protection, social sciences and humanities, radiobiology, patient associations.

5.2.2. Facilitate the broader implementation of detailed exposure characterisation for imaging procedures.

Patient dose from medical imaging exposure requires a paradigm shift from current practice. Currently, patient dose and associated risk estimation relies heavily on the use of effective dose. Effective dose represents a metric of equivalent radiation detriment compared to a uniform body irradiation based on organ weighting factors using a reference population. As such, it is not suitable for individual patient dose and risk estimation from non-uniformly irradiating techniques that can have markedly different dose distributions in different patients and human tissues. Other quantities such as computed tomography dose index (CTDI) provide a metric for quality control and technique comparison, rather than patient dose, and should not be used either as dose estimates for individual patients.

MEDIRAD has tested a methodology to estimate 3D patient dose distributions from CT examinations and extract organ doses based on patient-specific, equipment-specific and protocol-specific models. In addition, AI algorithms can be readily applied to support further research in patient-specific dosimetry estimations.

Potential areas and applications that will benefit from such development are: i) the estimation of rapid, "on-the-fly", personalised 3D dose distribution for every patient undergoing a CT or cone beam computed tomography (CBCT) scan, ii) estimation of dose in partially exposed organs, e.g., the liver during a chest CT examination, and iii) estimation of dose in patients with truncated field of view (FOV). Further work is needed on uncertainties that arise at various stages of the organ dose estimation procedure. Research in these fields will allow the development of real-time personalised dosimetry and its application in everyday clinical routine. As shown in MEDIRAD, dose evaluation is critical for various types of imaging procedures such as CT imaging, some interventional procedures, as well as nuclear medical imaging procedures, due to current regional and technological differences.

» Target audience: medical professional organisations, medical physicists, medical practitioners, scientific communities.

5.2.3. Conduct research determining indication dependent appropriate image quality.

Optimisation of currently available imaging procedures or evaluation of new imaging technologies in terms of benefit/risk ratios can only be performed in a meaningful way if an appropriate image quality for a given indication is guaranteed, and the influence of parameter changes on the image quality can be determined. Thus, it is necessary for relevant imaging procedures to find a consensus regarding clinically relevant image features and the required image quality on such features in terms of contrast, detail representation, sharpness, noise, and artefacts for a secure diagnosis. Within MEDIRAD, such consensus was achieved for unenhanced chest CT in the context of lung nodule detection, lung fibrosis, and mycobacterial infections. Obviously, there are many more clinical imaging indications, including unenhanced and enhanced CT imaging procedures, interventional imaging procedures, nuclear medical imaging procedures, and hybrids of these, which are relevant in terms of radiation protection research. The consensus on relevant image content and corresponding subjective quality parameters needs to be elaborated in future research projects on an international or at least European level. It is also a necessary prerequisite for the benefit/risk evaluation.

MEDIRAD also developed methods to determine objective image quality parameters directly in patient images and correlate the results of such parameters to the subjective image quality, through a large Europea-wide reader study. This approach provided important insight into the relevant image quality characteristics when determined in patient images for unenhanced chest CT examinations. This approach now needs to be further developed for all relevant clinical indications and imaging procedures, as stated above.

Similarly, the semi-automated tools developed by MEDIRAD for the objective image quality evaluation need to be further developed into fully automated tools suitable for online quality control and optimisation in the clinics, without adding to the workload of the clinical community. Suitable ways of presenting the results need to be further elaborated. AI based approaches for establishing automated image quality descriptors might be feasible and should also be investigated.

» Target audience: medical professional organisations, radiologists and nuclear medicine specialists, medical physicists, medical practitioners, scientific communities.

5.2.4. Promote implementation of combined exposure and appropriate image quality determination for optimising benefit/risk ratios in existing and new diagnostic tools.

Using unenhanced chest CT as an example, MEDIRAD has shown that it is feasible to evaluate individual patient exposure and corresponding image quality descriptors for the same examination and thereby provide a tool for optimisation of such imaging procedures. This was only feasible by integrating research approaches of radiologists, medical physicists, and radiographers. Optimisation in daily clinical routine will only happen if the approach is understood and easy to implement. The effect of changing parameters has to be clearly shown and the potential for individual patient-specific optimisation has to be presented.

MEDIRAD has shown that semi-automated approaches are feasible but must be further developed to fully automated tools that provide easy-to-understand results, if they are to be used broadly throughout Europe. Such tools need to use different characteristics, e.g. for image quality determination, but allow the same classification of images as well as the same indications for optimisation potential. Such aspects have to be taught to the medical practitioners through education and training programmes. Finally, ways need to be developed to implement such tools into legislation without increasing daily workload for practitioners, guaranteeing their use for optimised radiation protection on an individual patient basis. One option could be to develop the methodology of diagnostic reference levels into an advanced tool that performs all necessary documentation in a software-driven manner.

» Target audience: policy and clinical decision makers, scientific communities, medical practitioners.

5.3. MEDIRAD scientific achievements supporting these recommendations

- MEDIRAD had identified potential influencing factors and has also determined exposure characteristics for individual patients undergoing chest CT imaging.
- MEDIRAD has tested a methodology to estimate 3D patient dose distributions from CT examinations and extract organ doses based on patient-specific, equipment-specific and protocol-specific models.
- MEDIRAD also developed methods to determine objective image quality parameters directly in patient images and correlate the results of such para meters to the subjective image quality, through a large Europea-wide reader study.
- MEDIRAD has shown that it is feasible to evaluate individual patient exposure and corresponding image quality descriptors for the same examination and thereby provide a tool for optimisation of such imaging procedures.
- MEDIRAD has shown that semi-automated approaches are feasible.

4

Annex 1
Supporting evidence resulting from MEDIRAD research.

1. Recommendation 4.1 Promoting optimisation in radiation therapy: Deciphering biological mechanism of healthy tissue response, sensitivity and adverse effects

MEDIRAD clinical development of biological indicators of dose (blood PBMC) in nuclear medicine to assess the impact of low dose radiation exposure from 131I-NaI radioiodine ablation of thyroid cancer.

The time- and absorbed dose-dependent induction and repair of DNA double-strand breaks (DSBs) in peripheral blood mononuclear cells (PBMCs) after internal irradiation with radioiodine was investigated on 32 patients. Significant RIF reduction was observed after 50 mGy internal irradiation with I-131, after 4 hr and 24 hr. DNA damage was observed as nearly completely repaired after 24 hr. Repair rate is comparable to studies with external irradiation with gamma or X-rays. Sequential blood sampling was performed on 18 patients before and after administration of I-131 and whole body scans. Dose rate measurements were simultaneously provided. Continuous irradiation with decreasing but non-negligible dose rate in the patients leads to altered repair kinetics in vivo as there is, most likely, still DSB induction competing with repair.

MEDIRAD clinical identification of standard and innovative circulating biomarkers of radiation-induced cardiovascular toxicity from breast cancer radiotherapy.

The main objective is to define a biomarker profile for cardiac damage induced after breast cancer radiotherapy. It is expected that identification of relevant biomarkers from preclinical animal studies, validated in humans, if validated will lead to refined models of the risk of cardiac and vascular toxicity after low to moderate dose radiation exposure.

Gold standard/routine circulating biomarkers of myocardial injury (C protein, pro-BNP, high sensitive cardiac troponin I and T) were measured in serum/plasma of animal models and human patients before and after exposure to low dose radiation. New circulating biomarker candidates, such as microRNAs and extracellular vesicles (microparticles (MPs) and exosomes) were also measured and correlated/compared with the classical biomarkers of above and with the preclinical and clinical imaging data allowing quantify the myocardial injury severity.

Our preclinical studies have provided evidence of molecular changes in the plasma and whole blood of irradiated rats. Some of these changes appear to be dependent upon the dose and time point after radiation exposure. Importantly and linked to the above, preliminary statistical analyses have showed promising correlations between the biomarkers identified and cardiac function.

The clinical validation of standard and innovative blood biomarkers of radiation-induced cardiovascular toxicity is ongoing based on the multi-centric prospective cohort of breast cancer patients treated with radiotherapy at five centres (Netherlands, Germany, France, Portugal, and Spain). MEDIRAD EARLY HEART study included 200 patients. Currently statistical analyses are being performed to identify blood biomarkers of radiation-induced cardiovascular toxicity. Data of preclinical and clinical studies will be combined.

2. Recommendation 4.2 Facilitating innovation in artificial intelligence (AI) for personalised diagnostic and therapeutic protocols

Promote dosiomic approach based on optimised patient-specific 3D distribution of internal radiotherapy dose.

Within the scope of MEDIRAD, novel methodologies were developed to estimate personalised organ dose from chest CT examinations and hybrid examinations. Methodologies were based on personalised Monte Carlo (MC) simulations. Moreover, an image quality module was developed to be used in combination with the dosimetry tool for chest CT as well as for verifying that the images acquired provide a sufficient image quality for the diagnostic purpose. Towards clinical implementation, real time personalised dosimetric map generation is imperative.

The advent of sophisticated AI algorithms that will produce 3D dosimetric maps for each patient and provide dose information in segmented organs and other anatomical regions will greatly reduce the time required to estimate and assess individual patient dose and radiogenic risk (practically on-the-fly generation). Replacing the need of MC simulations with AI-based patient-specific 3D dose generation, renders the technique suitable for high patient-throughput, whereas suitable AI training schemes can mitigate current limitations in dose estimation for partially exposed organs and truncated FOV.

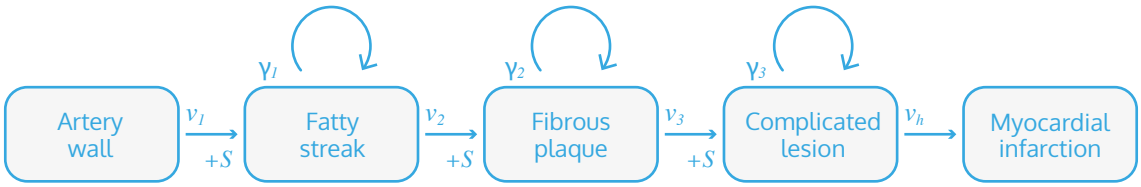
Promote development of radiomics supporting personalised medicine.

Within MEDIRAD, the EARLY HEART study showed that specific image markers from echocardiography, cardiac CT, cardiac MRI and circulating molecular biomarkers have the potential to early detect cardiac changes arising within the first 2 years after breast cancer radiotherapy. These biomarkers may help to identify, at the early stage, patients who may develop a cardiovascular effect due to breast cancer radiotherapy. If validated, these combined image and molecular biomarkers, radiomic approach, would be of great value to optimise patient follow-up.
A study protocol combining EARLY HEART and BRACE studies would take advantage of both enhanced knowledge for early cardiac changes and long term evolution of these early changes to develop preventive measures.

3. Recommendation 4.3 Modelling of radiation induced disease processes

Atherosclerosis is characterised by the progressive accumulation of lipids and fibrous elements in the walls of large arteries. Lipid deposition starts at preferred sites and results in atherosclerotic lesions. With time, the area involved with lesions increases and lesion appearance progresses. In the model, lesions are classified into three categories: fatty streaks, fibrous plaques, and complicated lesions. Main variables in the model are the percentages Fk of the coronary artery intimal surface area involved with these lesions.

The total percentage of the intimal surface area involved with any type of atherosclerotic lesions is denoted by F_1. The percentage involved with raised lesions, defined as fibrous plaques or more advanced lesions, is called F_2. Finally, F_3 relates to the most advanced, complicated lesions. Correspondingly, F_0 refers to the total, healthy or affected, intimal area of the artery wall. Risk was modelled to be proportional to the area involved with complicated lesions F_3. A schematic model representation is presented in the below Figure for the endpoint of myocardial infarction:



The percentages Fk are supposed to increase by two processes: formation of new lesions and growth of existing ones. As long as the lesion area is small, exponential growth is assumed with a growth rate γk, which is assumed to be normally distributed in the population. On the other hand, initiation of new lesions is assumed to be associated with the permeability or adhesiveness of individual endothelial cells and thus modelled stochastically. The probability of formation of a new lesion of stage k is assumed to be proportional to Fk-1[1,2].

[1] Simonetto C et al. Simulating the dynamics of atherosclerosis to the incidence of myocardial infarction, applied to the KORA population. Accepted by Statistics in Medicine. Circulated within MEDIRAD on 11.10.2019.

[2] Simonetto C et al. From atherosclerosis to myocardial infarction - a process - oriented model investigating the role of risk factors. Submitted. Circulated within MEDIRAD on 21.12.2020.

Within MEDIRAD project, a mathematical model on atherosclerosis and subsequent cardiovascular disease was developed within a new, versatile modelling approach. Based on individual information, several potential histories of disease development are simulated. This allows taking time-dependent cofactors, such as radiation exposure, into account.

Next, this process oriented model of atherosclerosis and subsequent ACEs was applied to a contemporary breast cancer cohort of 810 patient part of the BRACE cohort with measurements of coronary artery calcification. Patients with prior ischemic heart disease were excluded. For each disease stage in the model, association of model parameters with mean heart dose was tested.

The model reproduced the prevalence and associated risk of coronary calcifications (during a mean follow up of 9.1 years, 25 ACEs occurred). Mean heart dose significantly improved the fit only when implemented as affecting a late stage of atherosclerosis on already existing, complicated lesions (achieving $p = 0.007$). Therefore, an increase of ACEs few years after RT requires advanced atherosclerosis at the time of RT. At an earlier stage, calcified and non-calcified coronary plaques evolution from baseline before RT to 2 years after BC RT is under analysis in the EARLY-HEART study. According to the results, we will see whether EARLY-HEART study support these findings.

Partly based on these results, the calcified coronary plaques of the whole BRACE cohort (N=5825) are currently being delineated with a semi-automated segmentation method. The mechanistic model can be applied again to this larger cohort to validate the finding that ACEs few years after radiotherapy require advanced coronary plaques at time of RT. Furthermore, it will be studied whether volume of the calcified coronary plaques and/or dose distribution parameters of the calcified coronary plaques can further improve the prediction model for acute coronary events.

4. Recommendation 4.4 Implementing EU-wide epidemiological studies to enhance quality and safety of medical radiation applications

Foster interactions between clinicians, radiobiologists, physicists and epidemiologists to provide a clinical epidemiological framework for patient follow-up.

Within the MEDIRAD project, the BRACE study, a retrospective cohort study, consisted in the inclusion of more than 3000 breast cancer patients treated with radiotherapy between 2009 and 2013 with a mean follow-up of 9 years after radiotherapy; the EARLY HEART study, a multicentric prospective cohort study, consisted in the inclusion of 250 breast cancer patients treated with radiotherapy between 2017 and 2019 with a prospective follow-up of 2 years after radiotherapy.

The setting of these both cohorts involved collaboration between radiation oncologists, cardiologists, radiologists, radiobiologists, dosimetrists and epidemiologists.

These two clinical studies are still running, and our two preliminary conclusions underpin (i) the heart is an important organ-at-risk in breast cancer radiotherapy and should be spared as much as possible (ALARA-principle) and (ii) multivariable NTCP-models provide information on the excess risk of acute coronary events on an individual patient basis and can be used to decide if more advanced radiation technologies are indicated.

Moreover, within the MEDIRAD project, the setting up of the nested case-control study of cancer risk in the cohort of CT patients involved collaboration between oncologists, radiologists, epidemiologists, dosimetrists and radiobiologists.

Conduct patient follow-up after medical ionising radiation exposure by means of well-designed clinical epidemiological studies, focusing on most at risk populations.

MEDIRAD project focused on women who were irradiated for breast cancer, a procedure which results in substantial doses to the heart and vessels and hence this is a population at particular risk for radiation induced cardiovascular diseases. In the BRACE study, which aimed to model the risk of acute coronary event arising from few to 10 years after breast cancer radiotherapy, the results showed a dose-response relationship with whole heart doses and left ventricle doses.

In EARLY-HEART study, which aimed to identify cardiac changes arising within the 24 months after radiotherapy, the first results showed a dose-response relationship between subclinical left ventricular dysfunction (defined by a decrease in left ventricular global longitudinal strain 6 month after radiotherapy) and whole heart and left ventricular doses. These results remained to be confirmed with 24 month follow-up echocardiography data, and additional data based on cardiac CT and cardiac MRI still need to be analysed.

MEDIRAD project focused on populations of paediatric CT patients, chosen because exposure in childhood and adolescence tends to result in a higher risk of radiation induced cancer than exposure late in life. CT-scanning was chosen as one of the most common "higher-dose" diagnostic procedures. Results of the dose estimation in the study, showed that paediatric patients can receive doses of the order of 20-50 mSv to the brain from head CTs and varying between 2 and 20 mGy to the red bone marrow depending on anatomical region examined (head, chest or abdomen), age and time period of exposure.

Results of preliminary analyses of the nested case-control study in Sweden, based on a small number of cases suggest a dose-related increased risk of haematological malignancies which will need to be verified in the larger study. Results of the full cohort analysis are expected shortly.

Promote reliance on, and maintenance of, appropriate patient registries and secure mechanisms for linking data across registries for patient follow-up and dose optimisation, respecting patient privacy .

The cohort study in MEDIRAD was based on identification of patients and procedures from RIS and DICOM of specific hospitals and linkage with national/regional mortality and cancer registries. Difficulties were encountered in linking information from different hospitals (as patients could have received CTs in more than one) and, in some instances, with vital status and cancer registries because of the use of different patient identifiers in the different registries, particularly in early years.

The adequacy of the study could be much improved in the future through the use of common identifiers, the ability to link data from different registries within the same hospital (this was found to be difficult, particularly retrospectively) and across hospitals and should be much improved with careful digitalisation of patient registries and the setting up of adequate infrastructures to link them in a way that respects patient privacy.

Consider patient-specific dose modifiers in derivation of dose estimates as appropriate to different settings.

Within the MEDIRAD project, for all patients from BRACE and EARLY HEART study, individual patient 3-dimensional dose distributions were evaluated for the whole heart and cardiac substructures (including left ventricle) using previously published multi-atlas based auto-segmentation of the heart and these substructures in planning CT scans. For such methods based on multi-atlas, accuracy can be enhanced by taking into account patient specificities, such as breathing technique (free breathing or deep inspiration breath hold).

Within the MEDIRAD project conducted estimation of organ doses from CT scanning and other radiological procedures for patients in the cohort and the nested case-control studies. Doses varied substantially depending on the age at exposure (and assumed weight), with doses estimated for six different groups: New-born (0 to 3 months) with corresponding weight category (3-6 kg); 1 year (4 to 30 months) with corresponding weight category (7-13 kg); 5 years (31 to 90 months) with corresponding weight category (14-22 kg); 10 years (91 to 150 months) with corresponding weight category (23-42 kg); 15 years (151 to 210 months) with corresponding weight category (43-55 kg); adult (>210 months) with corresponding weight category (56+ kg).

Height and weight are additional important determinants of doses to specific organs but were not available for the subjects in the study. It will be important to obtain such information in the future, at least within case-control studies, in order to reduce uncertainties in dose estimates.

Increase capability for radiation dose tracking and managing programmes to provide relevant and standardised dose estimates.

The nested case-control study in Sweden conducted in MEDIRAD identified missing procedures for a number of subjects, even within a single hospital, which could have non-negligible impact on patient dose estimates. Comparison of RIS and PACS data in one of the hospitals in Spain, also identified inconsistencies in recording of procedures, and inconsistencies with the data available (in recent years) in the centralised image databases at the level of Catalonia.

In order to provide relevant and standardised dose estimates, these observations illustrate the need for improved radiation dose tracking and managing programmes, including all necessary technical parameters for dose calculation, in order to provide relevant and standardised dose estimates for clinical epidemiological studies.

Develop and validate biomarkers of diagnostic radiation exposure to better identify patient at risk of adverse effects.

MEDIRAD aims at identifying potential tissue markers of radiation sensitivity and radiation-induced cancer risk, based on a molecular epidemiological case-control study of haematological malignancies and brain tumours after paediatric CT scanning. Differentially expressed miRNA biomarkers were identified in glioblastoma tissue samples and in glioblastoma cell primary culture exposed to dose levels corresponding to CT scan exam. Analysis of the raw sequencing data identified six miRNAs found to be significantly altered (False Discovery Rate< 0.05) in glioblastoma tissue relative to normal brain tissue which were miR96-5p, miR1246, miR549a-3p, miR183-5p, miR183-3p, and miR182-5p. Our data was compared through meta-analysis with open source glioblastoma databases to select epigenetic non-coding RNA biomarkers potentially capable of predicting brain cancer initiation and progression.

These results, if confirmed with a bigger sample size, could suggest that patients with different radio-sensitivities would respond differently at low doses than after intermediate or high doses. For RS individuals, irradiation at intermediate or high doses should not be extrapolated to what happens at low doses. The implication of this possible effect on radio-induced cancer after low doses should be further elucidated.

Use results of clinical epidemiological studies to optimise treatment and imaging protocols and patients follow-up.

Within MEDIRAD, EARLY HEART study showed that specific image markers from echocardiography, cardiac CT, cardiac MRI, and circulating molecular biomarkers have the potential to early detect cardiac changes arising within the first 2 years after breast cancer radiotherapy. These biomarkers may help to identify, at the early stage, patients who may develop a cardiovascular effect due to breast cancer radiotherapy.

If validated, these combined image and molecular biomarkers would be of great value to optimise patient follow-up. A study protocol combining EARLY HEART and BRACE studies would take advantage of both enhanced knowledge for early cardiac changes and long term evolution of these early changes to develop preventive measures.

Harmonise data protection guidelines at the European level to facilitate EU-wide epidemiological studies in medical RP.

MEDIRAD experienced major delays due to the differences in implementation and interpretation of the GDPR, which varied across countries and even institutions within the same country. This effectively paralysed for several years the conduct of the cohort and case-control studies in Catalonia, despite these studies being recognised by the Director General of Public Health of the Department of Health as a public health priority and surveillance of the impact of diagnostic procedures in the patient population.

5. Recommendation 4.4 Optimising radiation based medical imaging procedures in terms of improved benefit/risk ratios and individualised procedures

MEDIRAD aims at facilitating the broader implementation of detailed exposure characterisation for imaging procedures such as computed tomography, hybrid imaging procedures and fluoroscopically guided procedures. Personalised 3D dose distributions for adult (203 patients) and paediatric (93 patients) populations undergoing diagnostic chest CT scans were generated using Monte Carlo (MC) computations. Individual clinical indications, such as pulmonary fibrosis, metastatic disease and other lung infections in adult population were considered. Patient-specific organ-doses were extracted and final results using regression analysis demonstrated that average organ doses and associated risks differentiate based on many parameters such as age, gender, clinical indication, body size, and exposure parameters.

The outcome of the study suggested that optimal patient management has to adhere to CT protocol dosimetric optimisation based on the aforementioned patient characteristics. This requirement for optimisation prompts further research on i) fast, automated, generation of three dimensional dosimetric maps for each patient undergoing a CT examination, and ii) fast and automatic extraction of organ-doses that can be readily used as indication of individual patient risk from a specific medical imaging procedure that uses ionising radiation. The European Union Basic Safety Standards states that the interventional radiology X-ray systems must be equipped with a device informing the practitioner of relevant parameters for assessing patient dose. MEDIRAD presented and validated a patient dose monitoring tool for fluoroscopically guided procedures based on a freely available MC code of photon transport (MC GPU) in a voxelised geometry. This tool provides the dose values at specific organs and positions as well as the dose distribution and the position of maximum dose. This dosimetric information is useful at multiple levels. Improvements in relevant technologies and guidelines around the appropriate use of these systems are required and should be anticipated soon.

Annex 2

Supporting evidence resulting from the stakeholder consultation process.

MEDIRAD stakeholder forum outcomes.

At the onset of the MEDIRAD project a stakeholder forum (SF) was established as a means of engaging in meaningful dialogue with a multidisciplinary group of representatives from the field of medical ionising radiation and associated protection research. The SF was consulted via a comprehensive questionnaire which aimed at ranking various broad-ranging approaches for optimisation of exposure to ionising radiation of patients and medical professionals and prioritise technical topics for inclusion in the current MEDIRAD recommendations.

Of the 86 SF members, there were 85 respondents to the questionnaire offering an interdisciplinary perspective from 69 nationals within Europe and 16 international representatives.

MEDIRAD stakeholder forum expectations.

Table 1
EUROPEAN STAKEHOLDERS' EXPECTATIONS: HIGH PRIORITY TECHNICAL TOPICS

Rank	Topics
1	Optimising image quality / dose during CT scans, including multimodality imaging procedures (e.g. SPECT-CT and PET-CT-scans).
2	Improved protocols aimed at reducing exposure whilst preserving or improving diagnostic quality/ therapeutic benefits (e.g. better accounting of potential secondary or late effects of healthy tissue exposure).
3	Optimising patient follow-up care after radiation therapy and collecting valuable epidemiological data through a better linkage of medical professionals from relevant disciplines.
4	Increasing education and training of medical professionals on radiation protection optimisation.

Table 2
EUROPEAN STAKEHOLDERS' EXPECTATIONS: INTERMEDIATE PRIORITY TECHNICAL TOPICS

Rank	Topics
5	Promoting individualised patient care in nuclear medicine. Procedure for evaluating patient-specific doses deliver to volumes and organs through activity uptake.
6	Improvement of target definition by better delineation of the target volume, better margins definition and better definition of the heterogeneity and of the biological volumes of the tumour at the voxel scale.
7	Modelling of patient dosimetry at the voxel scale. It is necessary to move from planned dose maps to delivered dose maps. (Treatment planning improvement, doses delivered during diagnostic and positioning imaging procedures, modelling simulations, clinical Decision Support System, Data standardisation and machine learning data base...).
8	Predicting quickly and accurately the response of tumours and normal tissues to ionising radiation using new multimodal and functional imaging and/or new biological and molecular surrogates. The development and validation of novel biomarkers will be required in order to develop treatment personalisation approaches.
9	Development of European registries of patient dose/imaging with recommended appropriate quantities (effective dose, organ dose) for radiological examinations.
10	Developing and validating operational biomarkers predictive of patient exposure – side or late adverse effects - following repeated radiological examinations, or radiotherapy protocols.
11	Optimising medical staff protection during interventional radiological procedures by ensuring proper availability and use of shielding equipment, while at the same time considering their actual effectiveness and efficacy.

Table 3
EUROPEAN STAKEHOLDERS' EXPECTATIONS: LOW PRIORITY TECHNICAL TOPICS

Rank	Topics
12	Technology development.
13	Future radiation protection research for radiation-oncology: Normal tissue response.
14	Development of European patient registries of dose/image/clinical diagnosis and patient follow-up, for the purpose of clinical procedure standardisation and radiation protection optimisation (European radio-vigilance).
15	Future radiation protection research for radiation-oncology: Combined treatment.
16	Modelling of patient dosimetry on an individual basis by highlighting the range of absorbed doses delivered from fixed administrations of activity, in order to evaluate the range of possible secondary effects, including long-term risks of secondary malignancies.
17	Future radiation protection research for radiation-oncology: Medical countermeasure.

Table 4
EUROPEAN STAKEHOLDERS' EXPECTATIONS: LOW INTEREST TECHNICAL TOPICS

Rank	Topics
18	Facilitating the development of large-scale multinational epidemiological studies by proposing guidelines to help European countries to implement at the national level European regulatory requirements on ethics (including compliance with GDPR directive).
19	Development of personalised protocols that factor in individual patient radiation sensitivity (e.g. via biomarkers of radiation sensitivity).
20	Exploring of the potential of patient-specific radiobiology tests to assess individual radio-sensitivity, in order to personalise treatment protocols.
21	Protocols to set up optimised imaging systems for quantitative imaging of I-131 irrespective of camera make or model.
22	Outlining a plan for a large-scale and multi-site epidemiological study to evaluate the effects of low absorbed doses of radiation as a result of nuclear medicine imaging procedures in a population with an expected normal life expectancy.
23	Consideration of individual bio-kinetics in patients with residual thyroid tissue or adjuvant disease, rather than reliance on models and values established for a healthy population.
24	Reinforcing regulations (e.g. by extending the scope of Diagnostic Reference Levels (DRLs) at the European level), and regulatory oversight (e.g. radiation protection experts, inspections).
25	Web/smartphone application for adverse effects.

For more information on the stakeholder consultation process and outcomes, see: M. Benderitter, E. Herrera Reyes, M.A. Benadjaoud, F. Vanhavere, N. Impens, U. Mayerhofer-Sebera, M. Hierath, J.R. Jourdain, G. Frija and J. Repussard. MEDIRAD formulation of science-based recommendations for medical radiation protection: a stakeholder forum survey. Radioprotection. 2021. 56(4), 275–285. doi: 10.1051/radiopro/2021030.

Annex 3

Stakeholder involvement in the development and implementation of Recommendations.

MEDIRAD Recommendations were elaborated on the basis of scientific findings from the research developed during the project, in consultation with stakeholder organisations which were invited to take part in the MEDIRAD Stakeholder Forum. This consultation process included an enquiry, based on on-line questionnaires aiming to identify priority concerns among stakeholder organisations, in the field of MEDIRAD scientific investigations, and a review of draft recommendations which were presented on-line to Forum members, and discussed at two workshops organised by MEDIRAD.

The list of MEDIRAD Stakeholder Forum members is provided hereafter. The publication of this list does not imply that the contents of MEDIRAD Recommendations are formally endorsed by these organisations. MEDIRAD Stakeholder organisations are invited to contribute to the dissemination and implementation of Recommendations or parts thereof, as they see fit within the limits of their missions and attributions.

MEDIRAD Stakeholder Forum Members, in alphabetical order:

· Associação Portuguesa dos Técnicos de Radiologia, Radioterapia e Medicina Nuclear
· Associazione Italiana di Radioprotezione Medica
· Associazione Italiana di Radioterapia Oncologica
· Associazione Italiana Medicina Nucleare
· Belgian SocieTy for Radiotherapy & Oncology
· Belgian Society of Radiology
· Biobank of Eastern Finland and University of Eastern Finland
· Bulgarian Society of Biomedical Physics and Engineering
· Bundesamt für Strahlenschutz (Federal Office for Radiation Protection)
· Cardiovascular and Interventional Radiological Society of Europe
· Commissariat à l'Energie Atomique et aux Energies Renouvelables
· Croatian Society of Radiology
· Czech Association of Medical Physicists
· Danish Health Authority, Radiation Protection
· Danish Society for Medical Physics
· Deutsche Gesellschaft für Biologische Strahlenforschung
· EFRS Educational Wing
· ESR EuroSafe Imaging
· ESR Patient Advisory Group
· European Network for Training and Education of Medical Physics Experts
· European Nuclear Education Network Association
· European Nuclear Education Network Association +project
· European Organisation for Research and Treatment of Cancer
· European Society for Vascular Surgery

· European Society of Medical Imaging Informatics
· European Society of Paediatric Radiology
· Federal Agency of Nuclear Control
· Federazione nazionale Ordini dei Tecnici di radiologia e delle professioni sanitarie tecniche, della riabilitazione e della prevenzione
· Finnish Advisory Committee for clinical audit
· Food and Drug Organization
· German Commission on Radiological Protection
· German Roentgen Society
· Greek Atomic Energy Commission
· Heads of the European Radiological Protection Competent Authorities
· Hellenic Society of Gastroenterology
· Hungarian Society for Medical Physics
· Institut National du Cancer
· International Agency for Research on Cancer, Section of Environment and Radiation
· International Atomic Energy Agency - Radiation Protection of Patients Unit
· International Commission on Radiological Protection
· International Organization for Medical Physics
· International Radiation Protection Association
· International Society of Radiographers and Radiological Technologists
· International Society of Radiology
· Irish Institute of Radiography and Radiation Therapy
· Irridium Network
· Istituto Nazionale per l'Assicurazione contro gli Infortuni sul Lavoro the National Institute for Insurance against Accidents at Work
· Italian Association for radiation Protection
· Italian Association of Medical Physics
· Kuopio University Hospital, Cancer Centre
· Lithuanian Association of Medical Physics and Engineering
· National Professional Association of Italian Qualified Experts
· Nordic Association of clinical Physics
· Nordic Working Group on Medical Applications
· Österreichische Röntgengesellschaft (Austrian Soicety of Radiation Protection)
· Plataforma Nacional de I+D en Protección Radiológica
· Quality Assurance Group in Radiotherapy
· Radiation Protection Association of Serbia and Montenegro
· Radiation Protection Officers working group on the West Coast of Norway
· Radiotherapy Translational and Preclinical Research network
· Romanian College of Medical Physicists
· Sociedad Española de Oncologia Radioterapica
· Società Italiana di Cardiologia
· Società Italiana di Cardiologia pediatrica e di cardiopatie congenite
· Società Italiana per la Radiologia Medica
· Societatea Română de Medicină Nucleară și Imagistică
· Société Française de Physique Médicale
· Société Française de Radiologie
· Société Française de Radiothérapie Onocologie
· Society and College of Radiographers
· St. James's University Hospital
· Superior Health Council
· Swedish Society for Medical Physics
· Swedish Society of Medicine
· Swiss Society of Radiobiology and Medical Physics
· University Hospital Leuven
· University of Arkansas
· University of California
· University of Eastern Finland
· University of Ghent
· University of Malta
· WHO network of Patients for Patient Safety

Annex 4

The MEDIRAD Project

Implications of Medical Low Dose Radiation Exposure.

A European multi-disciplinary project to enhance the scientific bases and practice of radiation protection in the medical field.

Coordinator	**European Institute for Biomedical Imaging Research (EIBIR), AT** **Coordinator contact: Monika Hierath, mhierath@eibir.org**
Scientific Coordination	**Prof. Elisabeth Cardis** **Barcelona Institute for Global Health (ISGlobal), ES**
Clinical Coordination	**Prof. Guy Frija** **Paris Descartes University, FR**
Duration	**1 June 2017 – 28 February 2022 (57 months)**
Total max EU Funding	**€9,995,145.75**
Website	**www.medirad-project.eu**

Ambition

MEDIRAD is a multi-disciplinary, cross-cutting project that aims to enhance the scientific bases and clinical practice of radiation protection in the medical field. MEDIRAD addresses the need to better understand and evaluate the health effects of low-dose ionising radiation exposure from diagnostic and therapeutic imaging and from off-target effects in radiotherapy. The MEDIRAD key research objectives are summarised in three pillars:

- **Pillar 1:** Development of innovative tools to increase the efficiency of future radiation protection research activities and support good clinical practice.
- **Pillar 2:** Improvement of the understanding of low-dose ionising radiation risks associated with major medical radiation procedures.
- **Pillar 3:** Development of recommendations based on research results and establishment of information exchange infrastructure to facilitate consensus.

Work plan

The MEDIRAD Project consisted of six interdependent and complimentary work packages (WP).

- **WP1:** Project management and dissemination: Scientific and clinical coordination, ethics management, knowledge management and exploitation, internal and external communication.
- **WP2:** Dose evaluation and optimisation in medical imaging: Optimisation of chest CT, interventional procedures and multimodality imaging, and development of imaging and radiation dose biobank.
- **WP3:** Impact of low-dose radiation exposure: Standardisation, biokinetic modelling and treatment planning, dosimetry, biomarkers of absorbed doses, protocol for epidemiological study.
- **WP4:** Breast radiotherapy and secondary cardiovascular risks: Epidemiological study on cardiovascular changes after radiotherapy, measuring markers of exposure and risk modelling.
- **WP5:** Possible health impact of paediatric scanning: Epidemiological study of paediatric CTs and cancer, including (epi)genetic biomarkers of possible sensitivity, dosimetry and statistical analyses.
- **WP6:** Bringing together medical & nuclear scientific communities: Formulation of science-based policy recommendations, consultation of stakeholders, organisation of dissemination seminars.

Impact

MEDIRAD will achieve significant progress in the interaction between the radiation protection and medical scientific communities at EU level, leading to cross-fertilisation of research efforts and the provision of more consolidated and robust science-based policy recommendations to decision makers in the respective sectors.

MEDIRAD will allow a better evaluation of the risks from radiation and better quantification of the necessary precautionary measures, leading to a more robust system of protection of patients, workers and the general public, whilst not unduly penalising activities through unnecessary and costly measures.

MEDIRAD will endeavor to positively modify the public perception of risks associated with ionising radiation thanks to the results of such combined nuclear and medical research.

MEDIRAD's long-term impacts are additional and improved practical measures for the effective protection of people in the medical and nuclear sectors.

Consortium

The multi-disciplinary consortium combines the expertise of 34 partners from 14 European countries. It includes major universities and research institutes as well as clinical partners.

· European Institute for Biomedical Imaging Research, AT
· Belgian Nuclear Research Centre, BE
· Ghent University, BE
· University of Geneva, CH
· Otto von Guericke University Magdeburg, DE
· University Medical Center of the Johannes Gutenberg University Mainz, DE
· Helmholtz Zentrum München German Research Center for Environmental Health, DE
· University Hospital of Würzburg, DE
· Philipps University of Marburg, DE
· University Hospital rechts der Isar of the Technical University Munich, DE
· Brandenburg Medical School, DE
· Barcelona Institute for Global Health, ES
· Polytechnic University of Catalonia, ES
· Autonomous University of Barcelona, ES
· Catalan Institute of Oncology, ES
· Paris Descartes University, FR
· Institute for Radiological Protection and Nuclear Safety, FR
· B-COM, FR
· French National Institute of Health and Medical Research FR
· Claudius Regaud Institute FR
· University of Crete GR
· University College Dublin, National University of Ireland, IE
· Sapienza University of Rome, IT
· Italian National Institute of Health, IT
· University Medical Center Groningen, NL
· VU University Medical Center, NL
· Netherlands Cancer Institute, NL
· Nofer Institute of Occupational Medicine, PL
· Polytechnic Institute of Coimbra, PT
· Cardiovascular Centre of the University of Lisbon, PT
· Region Västra Götaland, SE
· The Royal Marsden National Health Service Trust, UK
· University of Newcastle upon Tyne ,UK
· Imperial College London, UK

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