

## **The MOMENTUM study: an International Registry for the Evidence-Based Introduction of MR-guided Adaptive Therapy.**

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## **Abstract**

### ***Purpose/Objective:***

The Unity MRI guided Linear Accelerator (MR-linac, Elekta AB) is a state-of-the-art linear accelerator integrated with a 1.5T diagnostic quality MRI and an online adaptive workflow that can be used to deliver MR-guided radiation therapy (MRgRT). MRgRT allows for high-precision radiotherapy under real-time MR visualization. This enables margin reduction and subsequent dose escalation which may lead to higher tumor control and less toxicity. A prospective international registry was established to facilitate the evidence-based implementation of the Unity MR-linac into clinical practice and to aid further development of MR-linac-based MRgRT by long-term systematic evaluation of clinical outcomes.

### ***Methods and Results:***

In February 2019, the Multi-OutcoMe EvaluationN of radiation Therapy Using the MR-linac study (MOMENTUM) started within the MR-linac Consortium. The MOMENTUM study is an international academic-industrial partnership between several hospitals and the industry partner Elekta (Stockholm, Sweden).

For this study, all patients treated on the MR-linac are eligible for inclusion and are asked to share clinical data including patient, tumor and treatment characteristics, and technical patient data, defined as information generated by the MR-linac. The data are captured, pseudonomized, and stored in an international registry at set time intervals up to two years after treatment. Participants can choose to collect additional patient-reported outcomes and additional MRI scans on the MR-linac.

This registry will serve as a data platform that supports multicenter research investigating the MR-linac. Rules and regulations on data sharing, data access, and intellectual property rights are summarized in an Academic-Industrial Partnership Collaboration Agreement (AIC). Data Access Rules ensure secure data handling and research integrity for investigators and institutions. Separate Data Access Rules exist for academic and industry partners.

### ***Conclusion:***

The multi-institutional MOMENTUM study has been set up to collect clinical and technical patient data to advance technical development, and facilitate evidenced-based implementation of MR-linac technology with the ultimate purpose to improve tumor control, survival, and quality of life of patients with cancer.

### **Keywords:**

MRI, MR-linac, MR simulator, Functional Imaging, Radiotherapy, Magnetic Resonance Imaging, Image-guidance

## **Background and Rationale**

Radiotherapy is an important pillar in the multimodality treatment of cancer. Recently, MR-guided radiation therapy (MRgRT) has been introduced, enabling high-precision radiotherapy under real-time MRI visualization (1,2). Real-time visualization during MR-guided radiotherapy holds promise for margin reduction and dose escalation, which may lead to higher cure rates and less toxicity (3–5). The Unity MR-linac (Elekta AB, Stockholm, Sweden), integrating a 7 MV linear accelerator (linac) with a 1.5T diagnostic MRI scanner and an online adaptive workflow, enables MRgRT (6–10). The Elekta MR-linac received CE marking in June 2018, followed by FDA approval in December 2018 and Health Canada approval in March 2019, permitting commercial release and clinical implementation of this innovative device.

Technical innovations in radiation oncology, such as the MR-linac, are typically received with great enthusiasm by radiation oncologists and physicists, who are keen to see new technologies implemented in routine practice. Evidence supporting these new radiotherapy technologies is generally scarce (11). However, it is important to evaluate these novel and often costly technologies to gain insight into whether theoretical advantages are translated into actual patient benefits (12). In 2017, Verkooyen et al introduced the R-IDEAL framework as an assessment methodology for evidence-based clinical evaluation of innovations in radiation oncology (13). The R-IDEAL model, which was adapted from the surgical IDEAL framework, describes the clinical development process in six stages (14). The process starts with radiotherapy predicate studies (Stage 0), followed by first time use of the technology (Stage 1: Idea), technical optimization (Stage 2a: Development), proof of early clinical effectiveness and safety (Stage 2b: Exploration) and comparison of the innovation against standard care (Stage 3: Assessment). The final stage, Stage 4: Long-Term Evaluation, is crucial for post-marketing and surveillance purposes, and evaluates long-term outcomes.

In line with the R-IDEAL framework, The Multi-OutcoMe EvaluationN of radiation Therapy Using the MR-linac Study (The MOMENTUM study) was established. The goals of the MOMENTUM study are to aid and accelerate the development of anatomic and biologic MRgRT and to enable systematic evaluation of clinical outcomes of patients. Ultimately, the MOMENTUM study aims to ensure assessment of early effectiveness and safety of the MR-linac treatment, thereby facilitating the evidence-based introduction of the MR-linac into clinical practice. To further the methodological introduction, this registry is designed to serve as a data platform for future research investigating the MR-linac.

In this article we describe the MOMENTUM study, a clinical and technical patient registry, the governance structure, and the handling of patient confidentiality.

## Methods and Results

### Aims of the Momentum Study

The MOMENTUM study is a complex registry, integrating clinical and technical patient data.

The aim of the MOMENTUM study is to provide a data-infrastructure to:

1. Aggregate technical patient data in order to mature MR-linac software algorithms that drive the online adaptive workflow aiming to maximize the benefits of MRgRT.
2. Collect routine-care data for the evaluation of short- and long-term feasibility, safety, effectiveness, and toxicity of treatments on the MR-linac.
3. Create a repository of anatomical and biologic MRI data supporting Stage 0 of the R-IDEAL framework and aiming to develop MRgRT.

### The MR-linac Consortium

The MOMENTUM study was set up within the context of the international MR-linac Consortium, which currently consists of over 30 international centers (Figure 1) (15). Four European institutes, two institutes in the United States, one in Canada and the manufacturer of the MR-linac (Elekta AB, Sweden) were involved in the MOMENTUM project, and a professional public-private partnership manager (Lygature) (Table 1). Twelve Tumor Site Groups (TSGs) were established within the Consortium: brain, bladder, breast, cervix, esophagus, liver, lung, oligometastases, oropharynx, pancreas, prostate, and rectal cancer. The TSGs are international, cancer-specific expert panels aiming to develop and evaluate cancer-specific MR-guided treatment strategies. Main activities of these TSGs include preparing predicate studies and collaborative clinical trials that follow the R-IDEAL framework (13). As the MOMENTUM study is an ever evolving and expanding project, both the number of participating centers as the number of TSGs are likely to increase.

The MR-linac Consortium includes a Data Management Task Force (DMTF) which provides oversight and governance and manages the exchange of data according to the Data Access Rules. The DMTF includes oncologists, an Elekta employee, and an epidemiologist.

### The MOMENTUM study's Data Infrastructure

The MOMENTUM data infrastructure was created in accordance to the guidelines of Skripcak et al (2014), by an international expert panel that addressed the medical, information technological (IT), and legal aspects of the international data infrastructure separately before integrating them into one registry (figure 2) (16). According to Skripcak et al, the clinical value of a radiotherapy database relies on appropriate data management and data stewardship. The MOMENTUM study follows the FAIR criteria (e.g. data being Findable, Accessible, Interoperable and Reproducible) proposed by the Force 11 Group for databases to reach their full potential (17,18).

## I. Medical Component

### *Clinical Data*

For each patient in the MOMENTUM study, a core set of clinical data items is collected, consisting of patient and tumor characteristics and outcome data. These outcome data include toxicity and cancer status data such as recurrence, disease-free, and overall survival (table 2). Within the MOMENTUM study, patients have the option to provide patient-reported outcomes (PROs) through validated generic and disease-specific quality of life questionnaires. Additionally, the registry was customized to the requirements of each TSG by including TSG-selected and TSG-specific data items. These clinical data items (the core set, the TSG-specific and PRO data) are collected before, and three-, six-, and 24 months after treatment on the MR-linac. The clinical data are collected in parallel to routine clinical patient follow-up according to local standards of care.

### *Technical Patient Data*

Fundamental to any radiation therapy database is the collection of technical patient data such as imaging information, radiotherapy structures (contours), plans and dose information. The MOMENTUM study captures these data elements as well as others uniquely offered as a result of the novel, real-time MR-guided adaptive paradigm available on the MR-linac. Technical patient data, ultimately defined as data generated by the MR-linac during clinical operation, are captured after administration of radiotherapy on the MR-linac. Furthermore, researchers can collect extra research MRI scans during the treatment on the MR-linac of patients who consent to the optional research scans.

### *Clinical and Technical Patient Data Collection*

At every institution, dedicated clinical research coordinators collect clinical and technical patient data from the hospital information system. The information is pseudonymized on site before the coordinators upload the data into the MOMENTUM database. Each patient is assigned a unique study ID (study identification number) which facilitates the link between the technical and clinical patient data. Furthermore, this study ID is used in any future studies on the MR-linac, if applicable. This enables interconnection of all pseudonymized patient data throughout the Consortium whilst safeguarding patient confidentiality.

The study ID allocation is treatment-based, therefore the study ID relates to a radiation treatment course for individual patients. Multiple courses for a single patient are entered as separate events in to the database but the IDs are linked facilitating the identification of a single patient with multiple treatment courses.

## II. IT framework

### *Data Pooling Architecture*

The MOMENTUM clinical registry follows a centralized approach enabling secured virtual storage and easy uploading of data (16). The web-based clinical database (OpenClinica LLC, Waltham MA) is managed and governed by a senior data manager and hosted on a physical server from a neutral zone by the University Medical Centre (UMC) Utrecht.

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The technical database is hosted on the cloud (Microsoft Azure, Microsoft Corporation, Redmond, WA) and facilitates uploading of technical patient data, or DICOM data (Digital Imaging and Communications in Medicine) from all over the world. At every site, DICOM data are pseudonymized with the RSNA CTP (Radiological Society of North America Clinical Trial Processor) by a dedicated technical patient data custodian on an on-premise workstation. After pseudonymization, technical patient data are uploaded to the cloud via a secure transfer using Microsoft Fast Data Transfer (Microsoft Corporation, Redmond, WA). Data at rest are encrypted and accessible by researchers via secure VPN connection or virtual machines hosted on the cloud.

The clinical and technical repositories function as two separate entities for which the data are only connected through a unique study ID.

### *Data Interoperability*

Within the MOMENTUM study, we aim for maximum clinical and technical patient data interoperability according to the previously mentioned FAIR principles (18). The linked data are *Findable* for the collaborators of the Consortium within the two comprehensive databases. Straightforward data *Access* by researchers is realized through queries. Standard data elements defined by the DMTF and standardization of ontology, e.g. by implementing CDISC (clinical Data Interchange Standards Consortium) standards, TNM-O (Tumor-Node-Metastasis ontology), and ISO 860 (Data elements and interchange formats) are the foundation of the internationally integrated standard of information models effectuating data *Interoperability* within the MOMENTUM study (19). The MOMENTUM study captures a considerable amount of long-term data. These data can be used in future MR-linac studies which facilitates *Re-usage* of data. Furthermore, we aim to aid in formation of standardized international research protocols for future (non-) intervention studies performed on the MR-linac by serving as a data platform for these studies. This will minimize the probability of researchers conducting similar research on the MR-linac, which promotes efficient use, and re-usage of MOMENTUM data.

### *Quality Assurance*

Data quality is assured by using standardized electronic case report forms (eCRFs) and by the use of automatic validation and verification rules to reduce human error. Also, on-site training of the clinical research coordinators, standard operating procedures (SOPs), and monitoring (onsite and remote monitoring) will ensure data quality.

## III. Legal aspects

### *Legal Framework*

The MOMENTUM study has been set up as an academic-industrial collaboration managed by the impartial organization Lygature. This legal framework was selected because it best reflected the multi-pronged mission of clinical and technical development and clinical assessment. In addition, an academic-industrial partnership was felt to maximize transparency for academic and industrial collaborators and the value gleaned from early patient experiences.

### *Patient Confidentiality*

All patients over eighteen years old treated on the MR-linac are eligible for participation in the MOMENTUM study. They provide informed consent for the collection of their pseudonymized clinical and technical patient data. Participants can choose to collect additional patient reported outcomes and additional MRI scans on the MR-linac. Furthermore, participants from The Netherlands can choose whether or not they want to share their data with the industry partner.

### *Data Sharing, Data Governance and Data Access Rules*

The MOMENTUM study complies with national and regional data processing rules and regulations such as the European General Data Protection Regulation (GDPR), the USA Health Insurance Portability and Accountability Act (HIPAA), and the Canadian Personal Information Protection and Electronic Documents Act (PIPEDA). All rules and regulations on data sharing, data access and intellectual property are summarized in an Academic Industrial Collaboration Agreement (AIC) and signed for by the MOMENTUM partners.

Data access is regulated by the *Data Access Rules* which ensure secure, equitable and safe data handling whilst allowing for open international data exchange in accordance with the FAIR principles. The Data Access Rules are explicitly defined to facilitate research, encourage collaboration across the Consortium, and to safe-guard the interests and rights of institutional representatives, TSG representatives and primary investigators of future research performed on the MR-linac.

For academic partners we have developed a data request procedure for three different data request types (Table 3). Data requests for each institution's own data (Type 1 Academic Research Requests) will be granted without further review. Data requests that include patient data from multiple institutions are separated into requests that only include patients enrolled in MOMENTUM (Type 2 Academic Research Requests) and requests that contain patients that also participate in other studies performed on the MR-linac (Type 3 Academic Research Requests). The DMTF will review Type 2 and 3 requests for compliance to the 'institutional protection rule' stating that the requesting institution itself should have contributed significantly to the requested data. Furthermore, these Type 2 and 3 requests must also comply with the 'TSG protection rule' which ensures that these data requests do not compete with future research of TSGs. Finally, Type 3 Academic Data Requests will require additional approval for data access of patients co-enrolled into investigational MR-linac studies by the study's coordinating principal investigator (PI); the PI protection rule.

Data access by the industry partner, Elekta, is governed through separate Data Access Rules. Data requests from the industry partner are categorized into requests for technical, classifier and outcome data (Table 3). Classifier data includes patient, tumor and treatment characteristics and outcome data refers to toxicity and cancer control-related information. Data request by Elekta require a full description of the requested data elements, cohorts of interest and, the intended use of the data. Requests for technical patient data intended for non-academic purposes are fulfilled without further review by the DMTF. All data requests by Elekta that include classifier and/or outcome data must coincide with the

intentions of the data sharing proposal stipulated by the AIC. It is mandatory for the industry partner to have an academic partner involved in data requests relating to outcome data. Other data requests from the industry partner including classifier and/or outcome data require approval by all academic representatives of the DMTF.

### **Funding**

The MOMENTUM study is financially supported by Elekta AB and through in-kind contributions from all participating institutions. Conflicts of interest have been thoroughly addressed by recording academic and industry rights and obligations in the AIC, Data Access Rules and patient consent forms. By including Elekta as industry partner within the MR-linac Consortium ensures the integrity of the academic partners' intellectual property, publications and patient confidentiality. It is uncommon for commercial enterprises to invest in long-term evaluation allowing for identification of areas of the device that need improvement.

### **Discussion**

Increased digitalization and ongoing technical developments have resulted in the release of promising technical innovations into the medical field. Unlike new pharmacological agents, these innovations and devices undergo limited comparative evaluation before they are CE- or FDA-approved for release onto the market. Acquiring robust evidence to prove clinical superiority of new innovations over standard treatment strategies is challenging and expensive, therefore usually not feasible.

The European legal framework for medical devices has recently been changed by the European Medicines Agency (EMA) by adopting the Regulation (EU) 2017/745 on Medical Devices (20). By May 2020, the EMA's general safety and performance requirements for medical devices need to be clinically evaluated by manufacturers before the devices are deemed suitable to be released onto the market.

For example, usage of robotic surgery and proton beam radiation therapy (PBT) was purported to result in numerous theoretical clinical benefits for patients. As such, hospitals all over the world invested in expensive robotic surgery immediately after it acquired FDA approval (21). After all, it was expected to show higher rates of radical resections resulting in improved survival for cancer patients (21,22). It is known that robotic surgery reduces the duration of hospitalization and allows for faster recovery, yielding lower perioperative morbidity and mortality rates (23,24). However, standardized collection of outcomes of the surgical robot aimed at short- and long-term evaluation through the aid of a methodological framework could have accelerated and aided in objectifying these results.

Similarly the introduction of proton beam radiation therapy was not supported for the majority of tumor sites by evidence of superiority compared to standard photon radiotherapy (25). Level one evidence supporting proton therapy is lacking and most retrospective analysis failed to show superior oncological outcomes and even documented higher toxicity rates for some tumor sites (12)(26)(27). Mishra et al (2017) reported that only 7% of randomized clinical trials (RCTs) of PBT compare current radiation modalities and PBT illustrating the need for more level 1 research to PBT. According to Mishra et al,



the lack of comparative RCTs for PBT is partly explained by an insufficient number of proton facilities participating in research, thus a slow accrual rate (28).

Furthermore, a recent systematic review evaluating clinical studies on PBT found that only 20% of prospective trials reported on assessment of PROs (29). The MOMENTUM study provides standardized prospective collection of a core data set, including PROs, promoting consistent reporting of outcomes which facilitates accurate clinical evaluation.

The MOMENTUM study is a unique collaboration between academic and industry partners enabling a more systematic approach to the clinical implementation of the Elekta MR-linac. We hope to overcome some of the challenges we have seen during the introduction of previous new medical technologies by providing:

1. Standardized data sets of prospectively accrued data for patients treated with this new technology.
2. A methodology framework (R-IDEAL) which TSGs can adopt to demonstrate cancer specific applicability of the MR-linac treatments and ultimately compare MR-Linac treatment to standard radiotherapy treatments.
3. Easy and safe international data sharing between all partners, enhancing possibilities for collaborative studies.
4. A well-integrated and safe technical and clinical database designed by radiation oncologists.
5. One of only a few industry-funded collaborations aiming to critically analyze the device right at the start of clinical implementation.
6. A unique large scale academic and industrial partnership with all intellectual property rights and data sharing regulations recorded in a collaboration agreement (AIC). Therefore, facilitating industry sponsorship while maintaining an objective environment for academic partners to publish results and to enable Elekta to use pseudonymized technical data for the development of the MR-linac.

## **Conclusion**

The multi-institutional MOMENTUM study was set up to facilitate evidenced-based implementation of the Elekta MR-linac technology and to support its further technical development. The ultimate purpose is to improve tumor control, survival, and quality of life of cancer patients treated with radiation therapy. The registry was set up to facilitate the use of the R-IDEAL framework to evaluate the benefit of this technology and suitable indications for the MR-linac. This study will facilitate high quality research in the field of radiotherapy technology evaluation.

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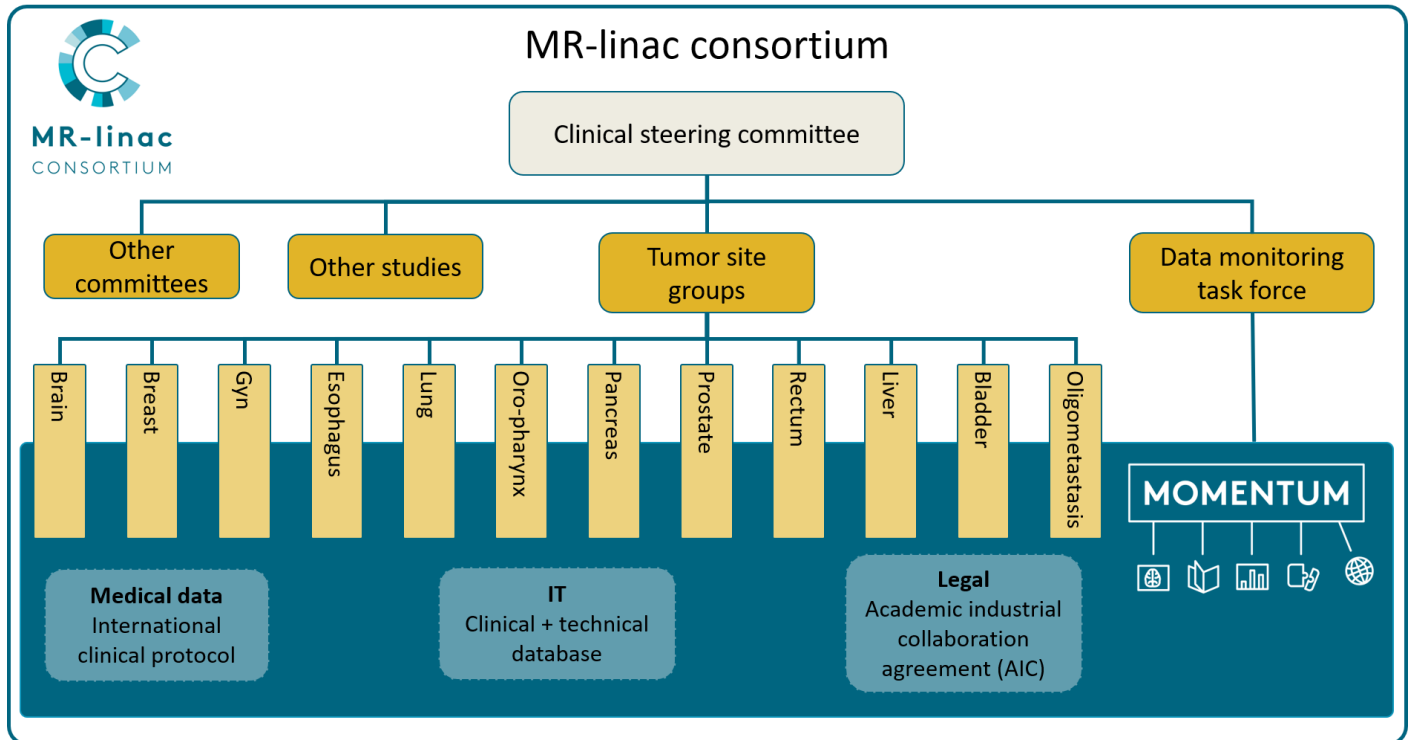
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Figures and tables - MOMENTUM



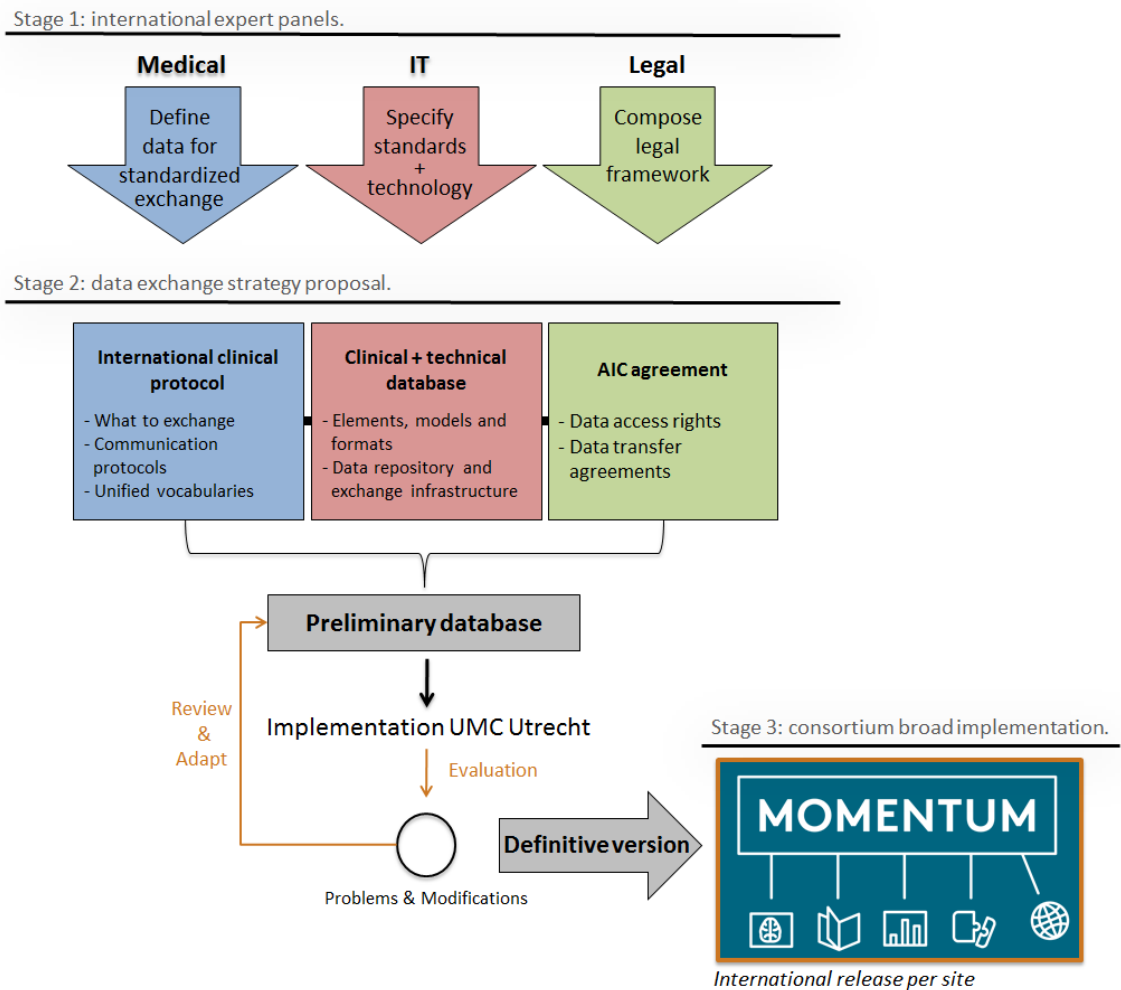
**Figure 1.** The MR-linac Consortium and its organizational structure. HCPC (Health Care Policy Committee), MAB (Methodology Advisory Board).

**Table 1.**

*Academic and industrial partners of the MR-linac consortium.*

<b>MR-linac Consortium Members</b>
<b>University Medical Center Utrecht, NL</b>
<b>The Netherlands Cancer Institute, Antoni van Leeuwenhoek Hospital, NL</b>
<b>Sunnybrook Hospital, CA</b>
<b>MD Anderson cancer center, US</b>
<b>Froedtert and Medical College of Wisconsin, US</b>
<b>The Royal Marsden NHS Foundation Trust and The Institute of Cancer Research, UK</b>
<b>The Christie Hospital, UK</b>
<b>Elekta AB, SE</b>
<b>Lygature Foundation, NL</b>

The MOMENTUM study: an International Registry for the Evidence-Based Introduction of MR-guided Adaptive Therapy.



**Figure 2.**

Working scheme for creating the MOMENTUM exchange strategy illustrating the stages of development: design (1), construction, testing and amendment (2), and release (3).

Abbreviations: IT (Information Technologies). This figure was reproduced and adapted from 'Creating a data exchange strategy for radiotherapy research: Towards federated databases and anonymised public datasets' by Skripcak et al (2014). Abbreviation: AIC Agreement (Academic Industrial Partnership Collaboration Agreement).

**The MOMENTUM study: an International Registry for the Evidence-Based Introduction of MR-guided Adaptive Therapy.**

**Table 2.**

Detailed data specifications of the clinical and technical data collected for the MOMENTUM study. Abbreviations: CD10 (international statistical classification of diseases and related health problems 10th revision). CDASH (clinical data acquisition standards harmonization). CDISC (clinical data interchange standards consortium). CRC (clinical research coordinator). CTCAE (common terminology criteria for adverse events). DICOM-RT (digital imaging and communications in medicine in radiation therapy). EQ-5D (standardized instrument for measuring generic health status). HIS (hospital information system). ICD-O (international classification of diseases for oncology). ISO 8601 (data elements and interchange formats – information interchange – representation of dates and time). MRL (MR-linac). NAACR (North American association of central cancer registries). NCI thesaurus (National Cancer Institute’s reference terminology and ontology). PACS (picture archiving and communication system). PROs (patient-reported outcomes). QoL questionnaires (quality of life questionnaires). RIS (radiology information system). RT (radiation therapy). SDTM (study data tabulation model). TG263 nomenclature (standardized nomenclature for radiation therapy). TNM-O (Ontology support for staging of malignant tumors).

Database	Information Type		Example	Source	Time of accrual	Data Elements & Info. model	Terminology & Ontology
OpenClinica	Classifier	Patient	Age, gender, Comorbidities	HIS	Baseline	SDTM CDASH CDISC	TNM-O
		Disease	ICD0 / ICD10, Histology, Biomarkers	HIS	Baseline		ISO 8601
		Treatment	Chemotherapy, Surgical intent, Total RT dose	HIS	End of treatment		EQ5D
	Outcome	Toxicity	CTCAE	HIS	3, 6 and 24 months FU		NCI
		Cancer control & PRO's	Local control, survival, QoL questionnaires	HIS + participant	3, 6 and 24 months FU		Thesaurus
						CTC-AE	
						TG263 - nomenclature	
Microsoft Azure	Diagnostic imaging data		Diagnostic CT, MR and PET imaging	PACS	End of treatment	DICOM-RT	Not applicable
	Radiotherapy planning data		Delineation/structure sets, planning CT	PACS, RIS	End of treatment		
	Radiotherapy delivery data		Motion data files, machine log files, fractions	PACS, RIS	End of treatment		



**Table 3.**

Data access rules for academic and industrial partners within the MOMENTUM study. Protection rules were implemented to ascertain acknowledgement of contributing institutions, tumor site groups (TSG) and principle instigators (PI) in data requests and intended publications.

Abbreviations: Data Management Task Force (DMTF), radiation therapy (RT), international classification of diseases for oncology (ICD-O).

## Data Access Rules MOMENTUM

### Academic Research Requests

Request	Definition	Procedure DMTF
Type 1	Institution's own data request	Granted without further review
Type 2	Multi-institutional data request	DMTF reviews - Institutional protection rule - TSG protection rule
Type 3	Type 2 request + data of patients enrolled in TSG' sub-studies	Conform type 2 request + - PI protection rule

### Industry Research Requests

Data class	Example	Procedure DMTF
Technical patient data	Imaging, RT structure sets	Granted without further review
Classifiers	Age, gender, ICD0, treatment	DMTF reviews - Publication intent
Outcomes	Toxicity, cancer control info	Conform classifiers request + - Involvement of academic partner
Classifier & outcome	Combination of the above	DMTF reviews - Details of requested data - Endorsement of a regulatory submission <i>Requires unanimous DMTF approval</i>