Contents lists available at ScienceDirect

Clinical and Translational Radiation Oncology

Original Research Article

Analysis of data to Advance Personalised Therapy with MR-Linac (ADAPT-MRL)

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ARTICLE INFO

ABSTRACT

Background: Analysis of Data to Advance Personalised Therapy with MR-Linac (ADAPT-MRL) is a multi-site, multinational, observational cohort registry designed to collect data on the use of the magnetic resonance linear accelerator (MR-Linac) for radiation therapy and patient outcomes. The registry will provide a linked repository of technical and clinical data that will form a platform for prospective studies and technology assessment.

Methods: Design: This registry aims to include an estimated 10,000 eligible participants across Australia and other countries over a 7- to 10-year period. Participants will undergo treatment and assessments in accordance with standard practice. Toxicity and survival outcomes will be assessed at baseline, during treatment, and with 3 monthly follow-up until 24 months, patient reported outcome measures will also be collected. Participants with a variety of cancers will be included.

Discussion: Data obtained from the ADAPT-MRL registry is expected to provide evidence on the safety and efficacy of the MR-Linac, a new technical innovation in radiation oncology. We expect this registry will generate data that will be used to optimise treatment techniques, MR-Linac software algorithms, evaluate participants' outcomes and toxicities and to create a repository of adapted plans, anatomical and functional MR sequences linked to participants' outcomes.

Introduction/rationale

The number of new cancer cases diagnosed in 2020 is estimated to be 150,000 [1] for Australia, and 1.8 million in the United States of America [2]. Radiotherapy is an important part of treatment involving the use of radiation for cure, or to reduce pain and other symptoms and is indicated in approximately 50% of cancer patients [3]. The fundamental goal of radiotherapy is to maximise the radiation dose delivered to cancer cells while minimising exposure to normal cells, which are often adjacent to cancer cells. Although survival rates for many cancers have been increasing in recent decades, not all cancers have been as responsive [4,5]. The survival rate for lung cancers has only increased

6% in the last 30 years [4], and survival rates for pancreas and high-grade brain cancers have not increased at all. Further, the challenge is not only improving survival, but also balancing the risks in a personalised way thereby minimising side effects and maximising cure and patients' quality of life. Technology is evolving at a rapid rate in response to this unmet medical need [6].

Magnetic resonance imaging (MRI) has advanced with improvements in image quality, tissue and functional visualisation capability, which inform clinical decision making and precision treatment. The linear accelerator first introduced in the 1950 s; a device that accelerates electrons to near speed of light energies and creates therapeutic X-rays for cancer treatment [7]. The pairing of MRI technology with the linear

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accelerator is an important recent innovation [8–11].

The promise of the MR-Linac is that radiation oncologists can visualise anatomical and functional changes during the course of radiotherapy and adapt the treatment plan to achieve optimal treatment.

With standard linear accelerators, the radiotherapy plan is based on a Computed Tomography (CT) scan completed days to weeks before treatment, and tumours can change or move in that time. Evidence has shown that movement of organs during a course of radiotherapy can lead to tumours being missed or normal organs receiving extra radiation [12]. To ensure tumours are not missed, it is necessary to treat large areas surrounding the cancer or perform invasive procedures to insert markers which can be tracked. Clearer visualisation of tumours and surrounding tissue through MRI; and adaptation to daily changes in tumour size, shape and location all mean treatment can now be delivered more accurately. This allows previously difficult areas to treat such as upper gastrointestinal tumours to be more accurately targeted while avoiding dose to healthy tissue and normal organs [13].

Historically, the innovations in radiation oncology, such as 3D conformal therapy, Intensity-Modulated Radiation Therapy (IMRT), and proton therapy have not followed a formal clinical development paradigm in the way that novel pharmaceuticals follow Phase I-IV clinical trial development [14]. As a result, the development and introduction of some innovations may have been unnecessarily delayed, and at the same time, the community has implemented new radiotherapy innovations
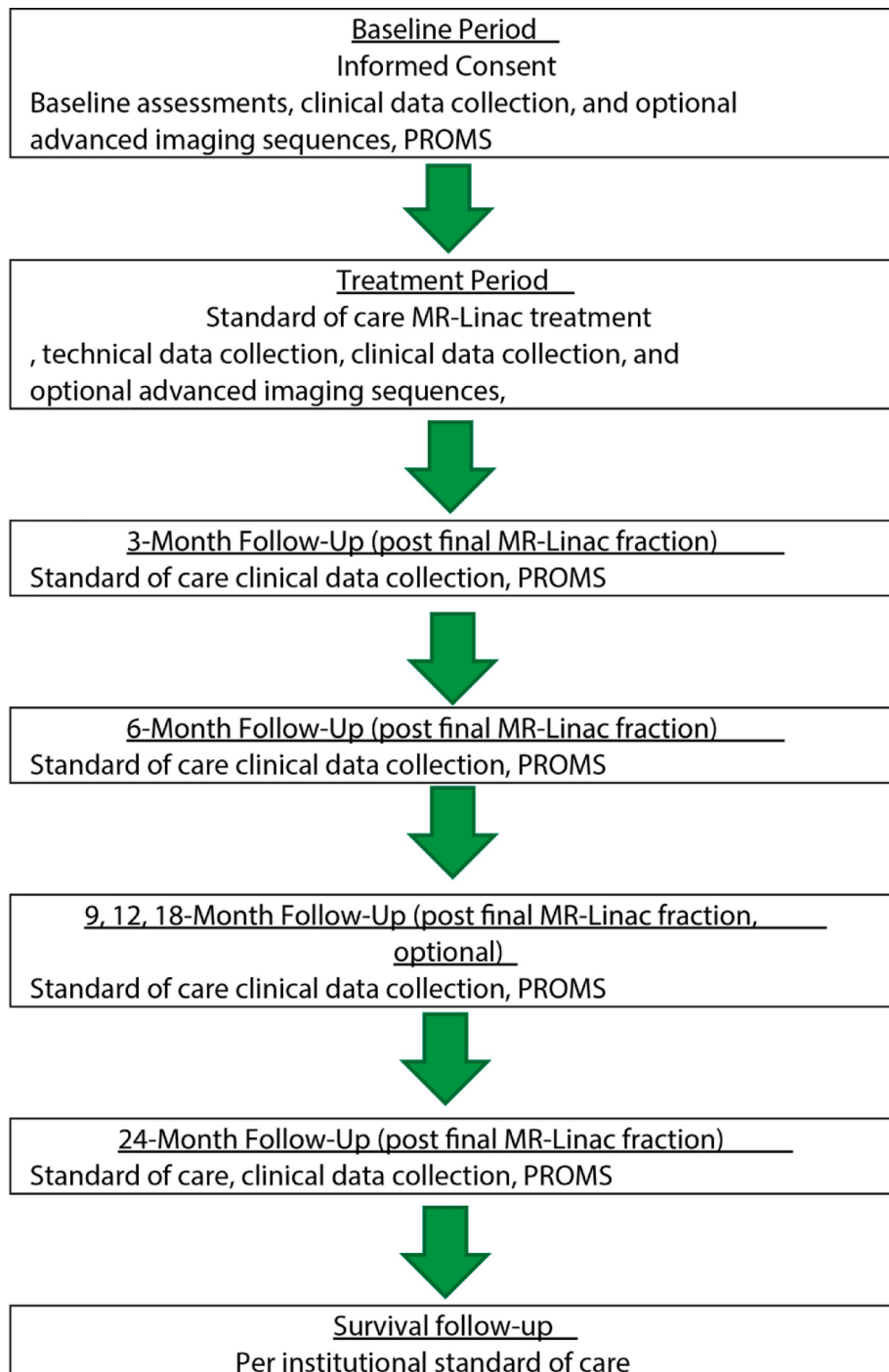

Fig. 1. Design of the ADAPT-MRL registry.

with no proven superiority compared to other treatments. Cognisant of this history, ADAPT-MRL is designed to support efforts to formally follow the Radiotherapy Idea Development Exploration Assessment Long-Term evaluation (R-IDEAL) framework as described by Verkooijen HM *et al* [16]. Adapted from the IDEAL framework for surgery, R-IDEAL is a stage-based process of developing and evaluation of radiotherapy innovations such as the MR-Linac. ADAPT-MRL will complement other MR Linac registries and master protocols currently open to assess this new technology [14,15]. In particular, ADAPT-MRL has been designed in coordination with investigators of The MOMENTUM Study, another multi-institutional observational registry of MR-Linac treatments, to enable efficient data aggregation and coordinated sub-studies [15]. ADAPT-MRL will provide a platform for technical and clinical studies, including hypothesis-testing and comparative studies, according to R-IDEAL recommendations. Registry-based studies (and cohort registries in particular) provide researchers with a system to collect and analyse exposure information and the associated downstream effects.

Design

Key selection criteria

Inclusion criteria

Participants 18 years old or older capable of giving informed consent who are scheduled for treatment on an MR-Linac device or have completed treatment on an MR-Linac device.

Exclusion criteria

Any standard of care eligibility requirement that would exclude a participant from receiving MR-Linac treatment.

Treatment description

ADAPT-MRL is a multicentre prospective and retrospective observational registry in participants scheduled to receive or who have received treatment with the MR-Linac. Participants will undergo treatment and assessments in accordance with their treating physician's standard practice. Technical and clinical data will be collected over the course of the registry. The expected accrual duration is 7–10 years. The duration of participation will vary for each participant depending on the number of fractions received. Participant outcomes will be continuously monitored by the MR-Linac Data and Safety Committee, which includes safety signal detection at any time during the Registry. Fig. 1 shows the overall design of the registry.

ADAPT-MRL is an open label, observational registry where participants and Registry personnel remain unblinded to the administered treatment and radiation dose. As the endpoints are objective, the probability of information bias is negligible.

Enrolment to the ADAPT-MRL registry is also not restricted by tumour type or stage. Therefore, the potential for selection bias is also considered low.

Given MR-Linac treatment is a relatively new modality, participants who have previously received MR-Linac treatment, as well as treatment naïve participants, can enrol in the registry. This minimises the outcome bias associated with only enrolling treatment naïve participants.

To minimise bias associated with participants that are lost to follow-up, registry personnel will ensure participants are contacted on a regular basis reminding them of upcoming treatments and follow-up visits.

A participant may withdraw from the registry at any time at his/her own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioural, or compliance reasons. This is expected to be uncommon.

At the time of discontinuing from the registry, an early discontinuation visit will be conducted. Assessments and further evaluations will need to be completed.

If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent unless there are circumstances justifying its removal.

If a participant withdraws from the registry, he/she may request destruction of any samples taken and not tested or any data collected but not yet used for analysis. The investigator must document this in the medical records.

Data collection

Participants will be assessed at baseline, during and on completion of treatment, 3 monthly follow-up until 24 months/end of Registry visit. Schedule of data collection is shown in Table 1. Figs. 2 and 3 describe the workflow setup in the oncology information system to facilitate data collection. All PROMs will be collected via Castor EDC (www.castoredc.com).

Optional advanced imaging sequences

Participants receiving treatment on the MR-Linac will be offered the option of providing advanced MR sequences (images) that are obtained before, during, or after treatment. It is estimated that the additional images will increase the total overall imaging time by up to 90 min and the scans are not considered standard of care. Participants will need to provide additional consent before these scan(s) commence. Images will be analysed in bulk to assess the relationship between imaging changes observed and the clinical participant outcomes.

Technical data collection

Technical participant data, defined as data generated by (the use of) the MR-Linac device will be collected (Fig. 4). A list of technical participant data elements is provided in Table 2.

Effectiveness and toxicity assessments

The following assessment will be used to evaluate treatment effectiveness:

- Disease-free survival
- Progression-free survival
- Survival rate
- Tumour specific assessments

Participants who display local and/or regional disease recurrence may have their post-failure diagnostic images exported as DICOM® files to delineate radiologically evident recurrent gross disease (rGTV) if readily available according to institutional practice. The data will include original planning dose, target volumes and recurrence imaging. Deformable image registration will then be applied to the rGTVs segmented on the recurrence images to convert them into "deformed rGTVs" on the planned images.

Treatment-related toxicities as defined by CTCAE V5.0 will be assessed via physical examination and medical history based on the tumour type and location.

Patient reported outcome measures

EQ-5D-5L and EORTC QLQ-C30 PRO questionnaires will be completed by all participants during baseline and follow-up visits. Additional questionnaires will be completed by participants based upon disease site (Table 3) and managed via Castor EDC online with paper back-ups available in clinic.

Data quality assurance

Prior to the initiation of the registry, relevant registry centre staff

Table 1
Schedule of Data Collection.

Assessment	Baseline	Treatment	Follow-up (quarterly)[5]	24 month[5]/early termination	Survival Follow-up
Informed consent[1]	X				
Inclusion/exclusion criteria	X				
Demographics	X				
Medical History	X				
Neoadjuvant, adjuvant & concomitant cancer treatments	X	X	X	X	
Commencement of Radiotherapy with MR-Linac[2]		X			
ECOG performance status	X		X	X	
EQ-5D-5L[3]	X		X	X	
EORTC-QLQ-C30[3]	X		X	X	
Additional tumour specific data and PROMs	X		X	X	
Toxicities (per CTCAE v5.0)	X		X	X	
Tumour response			X	X	
Technical Data Collection	X	X			
Optional Advanced Imaging Sequences	X	X			
Survival[4]		X	X	X	X

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events, ECOG = Eastern Cooperative Oncology Group, EORTC-QLQ = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire, EQ-5D-5L = EuroQoL-5 Dimension, PROM = Patient Outcome Measures.

[1] Informed consent is obtained prior to commencement of data collection for registry purposes and optional advanced imaging sequences.

[2] Details to be collected relevant to radiotherapy with MR-Linac includes treatment duration, region, treatment modality, planning technique, total dose, total fractions.

[3] Data will not be collected on the 9-month follow-up.

[4] Survival will be confirmed during the treatment period and each visit through to 24-months. Collection of survival data beyond 24-months will be completed per standard institutional practice.

[5] Follow-up visits at 3,6,9(optional),12(optional),18(optional) months through to 24-months will be scheduled from the last fraction administered to a participant.
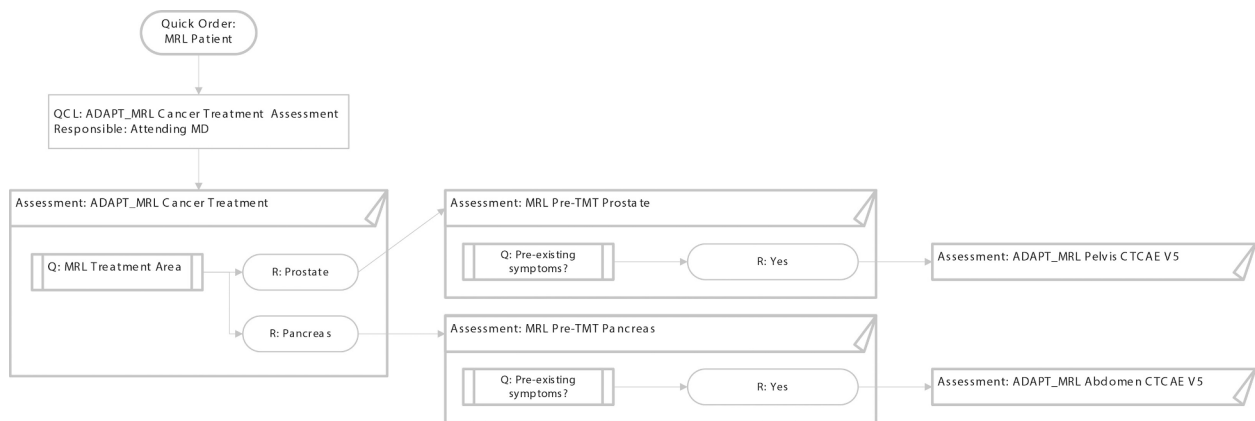

Fig. 2. Example Pre-treatment oncology information system (i.e. MOSAIQ, Elekta AB, Stockholm) workflow for Pancreas and Prostate.
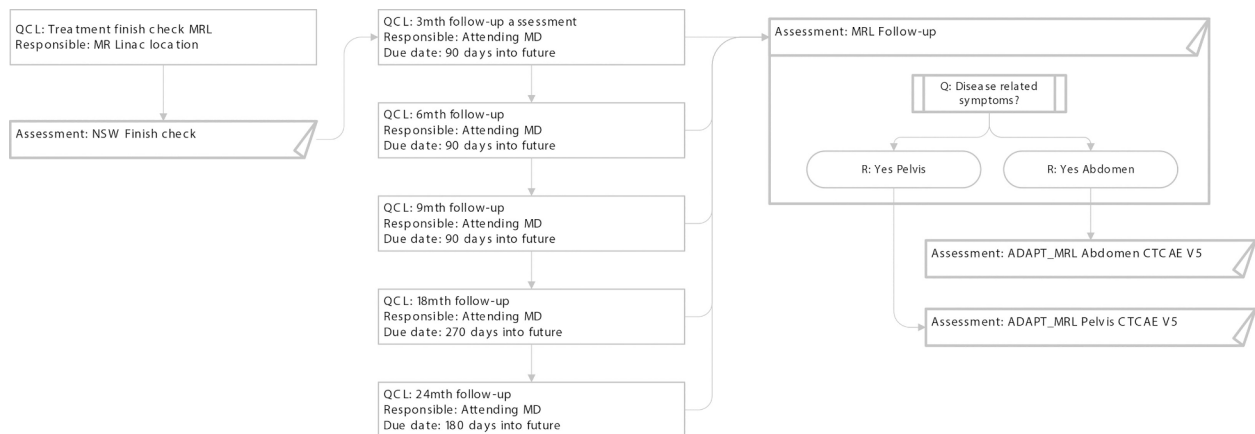

Fig. 3. Post treatment oncology information system (i.e. MOSAIQ, Elekta AB, Stockholm) workflow example.
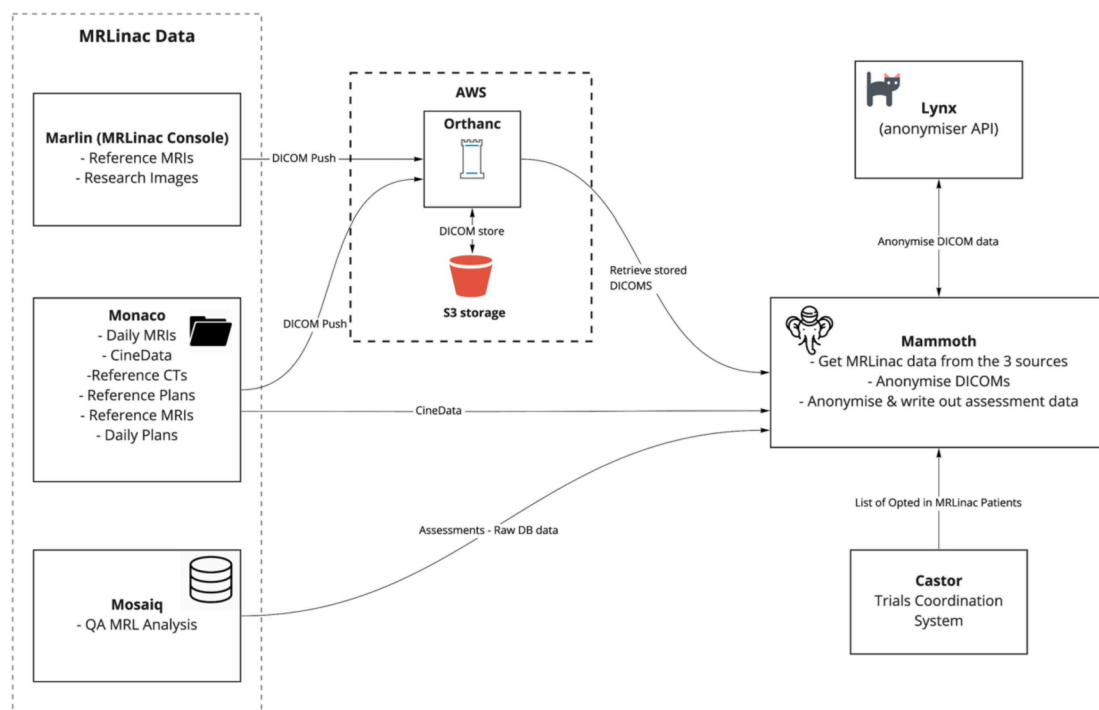
Fig. 4. Technical data collection, anonymization and storage infrastructure.

Table 2
Technical Data Collection.

Information	Time Points	Data Type
All named structures	Baseline	DICOM®-RTstruct
All radiotherapy plans and dose files	Baseline	DICOM®- RTplan, RTdose
Planning CT/MRIs	Baseline	DICOM® image
MRIs during treatment (pre-beam, beam-on, post-beam, research MRI)	End of Treatment	DICOM® image
Re-planning events	End of Treatment	DICOM®- RTplan, RTdose
Dose volume histograms	End of Treatment	Derived
Deformation vector fields	End of Treatment	Derived
2D Motion data	End of Treatment	Proprietary
Machine and treatment log files	End of Treatment	Proprietary
Linac and MRI QA	End of Treatment	Records

Table 3
List of cancer specific PROMs to be collected.

Site	PROMS
ALL patients	EQ5D-5L
	EORTC QLQ-C30
Prostate	IPSS
	IIEF5
	EORTC QLQ-PR25
Pancreas	EORTC QLQ-PAN26
Rectum	EORTC QLQ-CR29
Brain	EORTC QLQ-BN20
Breast	EORTC QLQ-BN23
Cervix	EORTC QLQ-GYN
Vagina	
Vulva	
Corpus Uteri	
Oesophagus	EORTC QLQ-OES18
Lung	EORTC QLQ-LC13
Oropharynx	EORTC QLQ-LC35

will be trained on the registry data collection requirements and the protocol. The registry centre personnel may contact the participants' referring doctors to request additional data to confirm baseline characteristics.

As part of the quality assurance process, audits and clinical data monitoring (remote and/or on-site) will be conducted on an ongoing basis. For each site, a Principal Investigator and a research coordinator will be assigned to ensure the registry is conducted in accordance with the protocol and ICH Good Clinical Practice requirements. Registry centres and registry documentation may be subject to audit during the registry by the sponsor or its nominated representative. In addition, inspections may be conducted by Human Research Ethics Committee/Institutional Review Board at their discretion.

Unexpected events, deviations, and violations will be reported in accordance with local institutional policies.

Data sharing and access policy

Anonymised data sharing and data security will be compliant with the applicable legal, regulatory, and ethical requirements for the regional jurisdiction in which ADAPT-MRL operates. Requests for access to data will be submitted to the ADAPT-MRL registry management committee. No information concerning the registry, or the data will be released to any unauthorised third party, without prior written approval of the sponsoring institution and execution of necessary third-party agreements as applicable.

Endpoints

Primary endpoints

- Survival rate – during treatment and at months 3, 6, 9, 12, 18 and 24
- Tumour response – clinical and pathological at month 24
- Disease-free survival – at months 3, 6, 12, 18 and 24

- Progression-free survival – at months 3, 6, 12, 18 and 24
- Treatment-related toxicities during screening and at months 3, 6, 9, 12, 18 and 24
- Change from baseline to months 3, 6, 12, 18 and 24 in EQ-5D-5L score
- Change from baseline to months 3, 6, 12, 18 and 24 in EORTC-QLQ-C30 score
- Change from baseline to months 3, 6, 9, 12, 18 and 24 in tumour-specific patient reported outcome measures (PROMs)
- Change from baseline to months 3, 6, 9, 12, 18 and 24 in ECOG performance status score.

Secondary endpoints

- Review of MRIs/CTs completed during the baseline and treatment period.
- Technical data: Dose volume histograms, deformation vector fields, 2-dimensional motion data and machine and treatment log files at end of treatment.

Statistics

The primary objective of the ADAPT-MRL registry is to assess participant outcomes following MR-Linac treatment. The secondary objectives are as follows:

- To provide technical participant data required to refine existing MR-Linac software algorithms
- To provide anatomic and biologic MR sequences to support both anatomic and response adapted Magnetic Resonance Image Guided Radiation Therapy (MRgRT).
- To collect clinical and technical data from participants who are concurrently enrolled into investigational studies, who will be flagged so that their clinical outcomes can be evaluated in accordance with those specific studies.

An estimated sample size of 10,000 participants will initially be included in the registry. The sample size for this registry is not based on a power calculation. It is believed that the proposed sample size will allow a reliable assessment to be made based on the statistics that will be generated to support the registry aims and outcomes.

Planned timeline

The expected accrual duration of ADAPT-MRL is 7–10 years. The duration of participation will vary for each participant depending on the number of fractions received.

Discussion

The MR-Linac, is a novel radiotherapy-delivery system that merits prospective evaluation based on its potential to affect cancer outcomes. The MR-Linac platforms include both a technological leap in hardware and advances in software that disrupt this historical paradigm by allowing real-time, online adaptation of the radiation treatment plan [17,18]. The improved soft-tissue contrast of MR imaging may allow for more accurate radiation planning and delivery hence minimise under-treatment and overtreatment, potentially translating to better disease control and fewer toxicities [19,20].

The ADAPT-MRL registry may facilitate improvements in functional and anatomical adaption of the MR-Linac by providing a linked repository of technical and clinical data that will form a platform for prospective studies and technology assessment. The data obtained from the registry will be used to optimise software, report treatment outcomes per disease site, report participants' toxicities and progression-free, disease-free, and survival rates. This data will also provide a platform

for registry-based studies.

The ADAPT-MRL registry aims to assess participant outcomes following MR-Linac treatment, provide technical participant data required to refine existing MR-Linac software algorithms and provide anatomic functional MR sequences to support both anatomic and functional Magnetic Resonance Image Guided Radiation Therapy (MRgRT).

Ethical and legal considerations

Ethics approval was granted by St Vincent's Hospital Human Research Ethics Committee (HREC), St Vincent's Hospital Sydney Research Office, St Vincent's Health Network, Translational Research Centre, Boundary Street, Darlinghurst, NSW 2010 on 17 July 2020, reference number 2020/ETHO 1414. Written informed consent will be obtained from all participants.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ctro.2021.09.004.

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