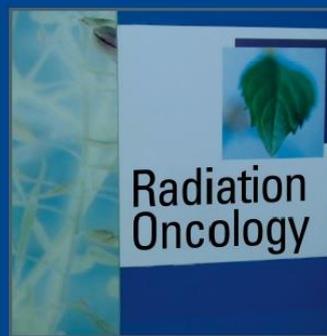


# CLINICAL STUDY PROTOCOL

## Study of MRI for Complex Pelvic Planning with Synthetic CT

(MARVEL – MRI only Anal canal, Rectum, cerVix and Endometrium radiation therapy  
planning)

Protocol Version 2.3 dated 23 August 2017

	<p><b>OUR VISION</b></p> <p>Achieving excellence in patient care by advances in treatment delivery, research and education</p> 	<p><b>OUR COMMITMENT</b></p> <ul style="list-style-type: none"><li>✔ To aim for quality improvements in our work practices and utilisation of technology</li><li>✔ To maintain effectiveness and efficiency in treatment delivery</li><li>✔ To optimise patient safety in clinical management and treatment</li><li>✔ To remain a centre of excellence for training and continuing education</li><li>✔ To grow our culture of research embedded in clinical practice</li><li>✔ To be recognised as amongst the best in the Nation by other Radiation Oncology Centres</li><li>✔ To acknowledge the contribution of patients, carers, families and all staff in achieving our vision</li></ul>
---	--	---

Author: Laura O'Connor      Date Created: 22/03/2017

Reviewed by: Jarad Martin, Peter Greer, Joanne Smart, Jason Dowling

Review Date: 23/08/17

UNCONTROLLED WHEN PRINTED

## Contents

Glossary of Terms .....	4
Administrative Information .....	5
1.1 Title .....	5
1.2 Trial Registration .....	5
2 Introduction .....	9
2.1 Background and Rationale .....	9
2.2 Why use MRI? .....	9
2.3 Problems with Current Workflow .....	9
2.4 Previous Work in This Area .....	10
2.5 Applying this Method to Complex Pelvic Cases .....	11
2.6 Aims .....	13
Study Design .....	14
Methods: Participants, Interventions, and Outcomes .....	14
Study setting .....	14
Participants .....	14
2.6.1 Eligibility Criteria .....	14
2.6.2 Exclusion Criteria .....	14
2.7 Interventions .....	15
<i>n/a</i> 15	
2.8 Outcomes/Endpoints .....	15
2.8.1 Primary .....	15
2.8.2 Secondary .....	15
2.8.3 Measurement variables and analysis metrics .....	15
2.8.4 Harm outcomes .....	16
2.9 Participant timeline .....	16
2.10 Sample Size .....	16
2.11 Recruitment .....	16
3 Methods: Data Collection, management and analysis .....	17
3.1 Data Collection Methods .....	17
3.1.1 Standard RO Structure Delineation .....	18
3.2 Data Management .....	19
3.3 Statistical Methods .....	19

Author: Laura O'Connor	Date Created: 22/03/2017
Reviewed by: Jarad Martin, Peter Greer, Joanne Smart, Jason Dowling	Review Date: 23/08/17
UNCONTROLLED WHEN PRINTED	

4	Methods: Monitoring.....	20
4.1	Data Monitoring.....	20
4.2	Harms.....	20
5	Ethics and Dissemination.....	20
5.1	Research Ethic Approval.....	20
5.2	Informed Consent.....	20
5.3	Confidentiality.....	20
5.4	Declaration of Interests.....	21
5.5	Access of Data.....	21
5.6	Ancillary and Post Trial Care.....	21
5.7	Dissemination Policy.....	21
6	References.....	22

<b>Author:</b> Laura O'Connor	<b>Date Created:</b> 22/03/2017
<b>Reviewed by:</b> Jarad Martin, Peter Greer, Joanne Smart, Jason Dowling	<b>Review Date:</b> 23/08/17
<b>UNCONTROLLED WHEN PRINTED</b>	

## Glossary of Terms

Term	Description/Meaning
CT Scan	Computed tomography scan. Three dimensional patient scan.
MRI	Magnetic resonance imaging. Type of imaging modality using strong magnetic fields, radio waves and field gradients to obtain a three dimensional image of the body with high tissue contrast.
Electron density	The density of the electrons which make up the tissues in the body. The treatment planning system needs this information to model attenuation of the radiation beam through the patient. For CT this is a simple calibration procedure. For MRI this is much more difficult.
Treatment planning system	A computer program set up by the medical physicists that models planned beams and calculates the dose for treatment. The system allows the radiation therapist to determine beam arrangements that give a high dose to the target while sparing normal tissues.
Hounsfield Units	The measured attenuation coefficients within a computed tomography scan – represented as a grey-scale
Dose	In radiation therapy this is the energy absorbed per unit mass from the radiation beam.
Dose distribution	The treatment planning system model of how the radiation dose is falling within the tissues of the body, derived from the planning beam data, electron density information and the planned beam arrangement.
Synthetic CT (sCT)	Artificially created CT scan produced from the MRI scan data
3D Gamma analysis	A comparison of the dose within one dose matrix (e.g. synthetic CT scan) with dose within another dose matrix (e.g. conventional CT scan). It compares the dose difference as well as the distance-to-agreement. It produces a Gamma value for each voxel. Values less than 1 are “pass.”
T2 TSE weighted MRI sequence	Conventional sequence used to visualise soft tissue structures for rectal or anal disease.
T2 SPACE weighted MRI sequence	Conventional sequence used in the creation of sythetic CT scan.
Target volume	A treatment volume outlined by the radiation oncologist with which a dose is to be prescribed to (usually the tumour volume and areas of risk of spread).
Organs at risk (OARs)	The surrounding organs which are adjacent or

Author: Laura O'Connor      Date Created: 22/03/2017

Reviewed by: Jarad Martin, Peter Greer, Joanne Smart, Jason Dowling

Review Date: 23/08/17

**UNCONTROLLED WHEN PRINTED**

	nearby the target volume to which the dose is to be spared.
Deformable registration	A mapping process involving the process of finding a point to point correspondence between positions on two different medical scans in order to establish a correspondence between the two images.
Image-guidance	This is the process where the beams are directed at the treatment volume. Images are first acquired either CT or x-ray that show the bony anatomy and/or soft tissue anatomy in order to match to the original planning scans. The patient is then moved into position using the couch until the treatment volumes are positioned correctly relative to the beams.
ConeBeam CT (CBCT)	A image-guidance process utilised on treatment. The x-ray generator and detector rotate around the patient in order to create a computed tomography scan (CT). This images the soft tissue within the body to be used to match to the original CT scan in order to target the treatment volumes.
Fluence/ fluence maps	The individual intensity profiles of the treatment beams. This is a representation of the number of photons to enter a cross sectional area. It is these fluence maps which, when applied to a patient, creates a dose distribution within the patient's body. As treatment techniques become more complex so do the corresponding fluence maps

## Administrative Information

### 1.1 Title

MARVEL – MRI only Anal canal, Rectum, cerVix and Endometrium radiation therapy pLanning

### 1.2 Trial Registration

Department of Radiation Oncology, Calvary Mater Newcastle Identifier: CMNDRO-1702  
 HNEHREC Reference No: 17/06/21/3.02

### Protocol Version

Protocol Version Number: Version 2.3

Date: 23/08/17

<b>Author:</b> Laura O'Connor	<b>Date Created:</b> 22/03/2017
<b>Reviewed by:</b> Jarad Martin, Peter Greer, Joanne Smart, Jason Dowling	<b>Review Date:</b> 23/08/17
<b>UNCONTROLLED WHEN PRINTED</b>	

## Funding

This study is funded by the Calvary Mater Newcastle Margaret Mitchell Research Grant 16-12.

## Roles and Responsibilities

Name: Title / first name / family name	Ms Laura O'Connor
Qualifications & employment position:	BMedRadSci(RT) Research Radiation Therapist
Organisational unit & mailing address:	Radiation Oncology Calvary Mater Newcastle, Locked Bag 7, Hunter Region Mail Centre, NSW 2310
Telephone and Fax:	Ph: 4014 3618 Fax: 4014 3169
Email address:	Laura.O'Connor@calvarymater.org.au
Role:	Principal Investigator. MRI patient data acquisition. Treatment planning. Overall project management and coordination.

Name: Title / first name / family name	Professor Peter Greer
Qualifications & position held:	BSc, MSc, PhD Principal Physicist
Organisational unit & mailing address:	Radiation Oncology, Calvary Mater Newcastle Locked Bag 7 Hunter Region Mail Centre NSW 2310
Telephone and Fax:	Ph: 4014 3689 Fax: 4014 3169
Email address:	Peter.Greer@newcastle.edu.au
Role:	Project supervisor investigator. Data analysis and publication.

Name: Title / first name / family name	Dr Jason Dowling
Qualifications & position(s) held:	PhD Research Leader - Biomedical Informatics
Organisational unit & mailing address:	CSIRO Health and Biosecurity Level 5 UQ Health Science Building 901/16 Herston, QLD, 4029
Telephone and Fax:	Ph: 07 3024 1658, Fax: 07 3024 1690
Email address:	Jason.Dowling@csiro.au
Role:	Project supervisor. Creation of substitute CT scans. Data analysis. Publication.

Name: Title / first name / family name	Dr Jarad Martin
Qualifications & position(s) held:	MB ChB, FRANZCR, DMed(Research) Staff Specialist, Radiation Oncologist

<b>Author:</b> Laura O'Connor	<b>Date Created:</b> 22/03/2017
<b>Reviewed by:</b> Jarad Martin, Peter Greer, Joanne Smart, Jason Dowling	<b>Review Date:</b> 23/08/17
<b>UNCONTROLLED WHEN PRINTED</b>	

Organisational unit & mailing address:	Radiation Oncology, Calvary Mater Newcastle, Locked Bag 7, Hunter Region Mail Centre, NSW 2310
Telephone and Fax:	Ph: 4014 3631 Fax: 4014 3169
Email address:	Jarad.Martin@calvarymater.org.au
Role:	Project supervisor. Patient recruitment. Clinical oversight. Patient plan approval. Assistance with analysis and publication.

Name: Title / first name / family name	Associate Professor Helen Warren-Froward
Qualifications & position(s) held:	BSc, PhD Associate Professor
Organisational unit & mailing address:	School of Health Sciences University of Newcastle Callaghan Campus
Telephone and Fax:	Ph: 4921 7142
Email address:	Helen.Warren-Forward@newcastle.edu.au
Role:	Project supervisor. Assistance with analysis and publication

Name: Title / first name / family name	Ms Haylea Richardson
Qualifications & employment position:	BMedRadSci (Radiation Therapy) Grad Cert HealthSci (Medical Radiation Science) Research Radiation Therapist
Organisational unit & mailing address:	Radiation Oncology, Calvary Mater Newcastle, Locked Bag 7, Hunter Region Mail Centre, NSW 2310
Telephone and Fax:	Ph: 4014 3618 Fax: 4014 3169
Email address:	Haylea.Richardson@calvarymater.org.au
Role:	MRI patient data acquisition. Treatment planning.

Name: Title / first name / family name	Dr Geetha Govindarajulu
Qualifications & position(s) held:	MBBS, MD, DNB, DPall Care, FRANZCR, Staff Specialist, Radiation Oncologist
Organisational unit & mailing address:	Radiation Oncology, Calvary Mater Newcastle, Locked Bag 7, Hunter Region Mail Centre, NSW 2310
Telephone and Fax:	Ph: 4014 3631 Fax: 4014 3169
Email address:	Geetha.Govindarajulu@calvarymater.org.au
Role:	Patient recruitment. Clinical oversight. Patient plan approval.

Name: Title / first name / family name	Dr Anne Capp
Qualifications & position(s) held:	DRANZCR, FRCR, MMed (Clin Epi)

<b>Author:</b> Laura O'Connor	<b>Date Created:</b> 22/03/2017
<b>Reviewed by:</b> Jarad Martin, Peter Greer, Joanne Smart, Jason Dowling	<b>Review Date:</b> 23/08/17
<b>UNCONTROLLED WHEN PRINTED</b>	

	Staff Specialist, Radiation Oncologist
Organisational unit & mailing address:	Radiation Oncology, Calvary Mater Newcastle, Locked Bag 7, Hunter Region Mail Centre, NSW 2310
Telephone and Fax:	Ph: 4014 3631 Fax: 4014 3169
Email address:	Anne.Capp@calvarymater.org.au
Role:	Patient recruitment. Clinical oversight. Patient plan approval.

Name: Title / first name / family name	Dr Mahesh Kumar
Qualifications & position(s) held:	MD, DNB, FRANZCR, Staff Specialist, Radiation Oncologist, Director of Radiation Oncology
Organisational unit & mailing address:	Radiation Oncology, Calvary Mater Newcastle, Locked Bag 7, Hunter Region Mail Centre, NSW 2310
Telephone and Fax:	Ph: 4014 3632 Fax: 4014 3169
Email address:	Mahesh.Kumar@calvarymater.org.au
Role:	Patient recruitment. Clinical oversight. Patient plan approval.

Name: Title / first name / family name	Dr Swetha Sridharan
Qualifications & position(s) held:	BSc, MBBS, FRANZCR, Staff Specialist, Radiation Oncologist
Organisational unit & mailing address:	Radiation Oncology, Calvary Mater Newcastle, Locked Bag 7, Hunter Region Mail Centre, NSW 2310
Telephone and Fax:	Ph: 4014 3631 Fax: 4014 3169
Email address:	Sweth.Sridharan@calvarymater.org.au
Role:	Patient recruitment. Clinical oversight. Patient plan approval.

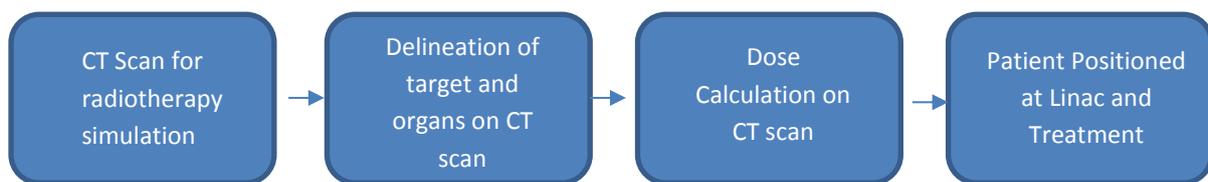
Name: Title / first name / family name	Ms Leah Best
Qualifications & position(s) held:	Senior MRI Radiographer
Organisational unit & mailing address:	Radiology Department Hunter New England Health Care Calvary Mater Campus
Telephone and Fax:	Ph: 4014 4674 Fax: 4014 4601
Email address:	Leah.Best@hnehealth.nsw.gov.au
Role:	MRI scanning at Calvary Mater Newcastle.

<b>Author:</b> Laura O'Connor	<b>Date Created:</b> 22/03/2017
<b>Reviewed by:</b> Jarad Martin, Peter Greer, Joanne Smart, Jason Dowling	<b>Review Date:</b> 23/08/17
<b>UNCONTROLLED WHEN PRINTED</b>	

## 2 Introduction

### 2.1 Background and Rationale

Radiation therapy (RT) is a primary treatment modality for rectal, anal and gynaecological cancer<sup>1-3</sup>. Calvary Mater Newcastle provides curative, external beam radiation therapy for 80-90 rectal, anal canal and gynaecological patients each year. CT scanning is the standard imaging modality for RT planning, providing tissue density information required by the planning system to calculate the dose for treatment (Figure 1). However tumour and soft tissue contrast is limited on CT scans and additionally this modality exposes the patient to potentially unnecessary radiation<sup>4</sup>.



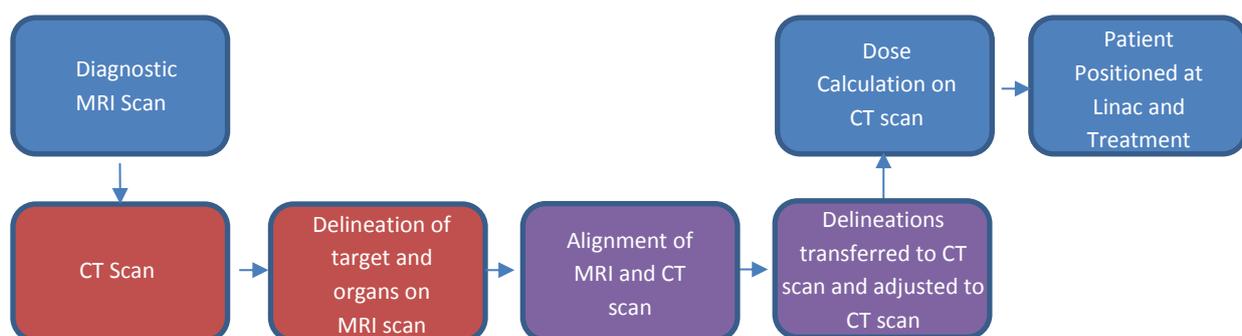
**Figure 1 Simple CT based radiation therapy workflow. The patient is first CT scanned; the radiation oncologist delineates the target and the organs at risk on the CT scan. Dose is then calculated on the CT scan. Patient is treated on the linear accelerator (linac).**

### 2.2 Why use MRI?

Magnetic resonance imaging (MRI) scanning in radiation therapy planning has been used on a routine basis over the past decade. Its superior soft tissue contrast, when compared to CT, allows for much more precise delineation of tumour target volume and organs at risk<sup>4</sup>. It also has the added benefit of being deemed as a ‘safer’ imaging modality as it uses magnetic fields rather than ionizing radiation to image the body.

### 2.3 Problems with Current Workflow

At present, rectal, anal canal and gynaecological cancer patients undergo an MRI as part of their diagnosis and staging pathway<sup>5</sup>. This MRI is then aligned to their planning CT scan as it aids in tumour localisation (Figure 2). The difficulties faced with this process however, is that the patient is positioned differently for their diagnostic MRI than they are for their radiotherapy planning CT scan. This introduces inaccuracies in the alignment process which makes the translation of tumour location difficult between the scans and adjustments need to be made to account for this.



<b>Author:</b> Laura O'Connor	<b>Date Created:</b> 22/03/2017
<b>Reviewed by:</b> Jarad Martin, Peter Greer, Joanne Smart, Jason Dowling	<b>Review Date:</b> 23/08/17
<b>UNCONTROLLED WHEN PRINTED</b>	

**Figure 2 Current CT-MRI based radiation therapy workflow. The MRI scan is used for delineation and must then be aligned to the CT scan. The delineations are transferred to the CT scan and then dose calculation is performed.**

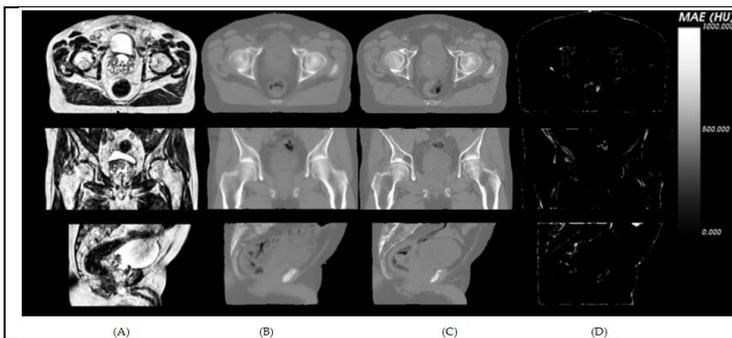
The planning CT scan is acquired with the patient immobilised in the position that is required for radiotherapy treatment. This project proposes that participants also undergo a MRI in the treatment position at the time of their planning CT scan. If proven to be a successful workflow option in this study, it is our aim that the planning position MRI scan would ultimately replace the need for the planning CT scan. The MRI will be of greater use in tumour delineation than in the current workflow as there will be no adjustments needed to the treatment volumes. Due to the superior soft tissue contrast, **MRI only** radiation treatment planning has the potential to improve radiotherapy planning for this cohort of patients as well as having the additional benefit of reducing the patients radiation exposure<sup>4</sup>.

## 2.4 Previous Work in This Area

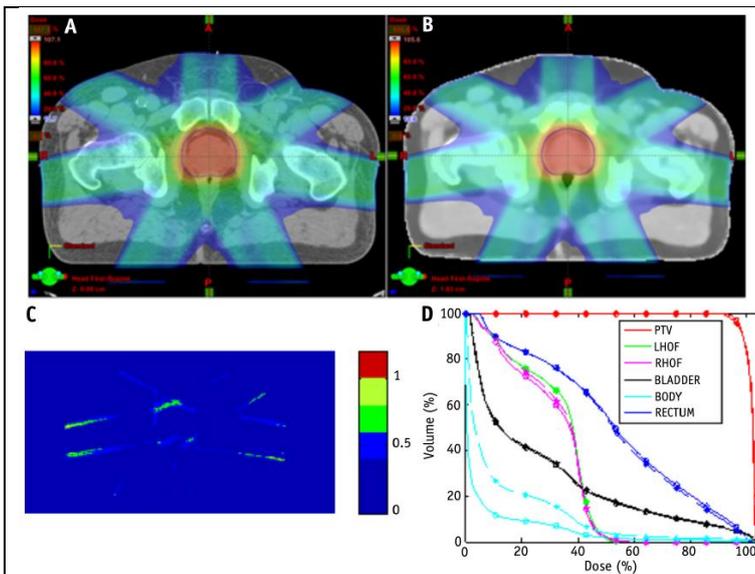
Due to the associated benefits of using MRI in radiation therapy, there has been a good deal of work in developing ways in which MRI can be applied to radiation therapy treatment planning. Researchers have developed varying methods to define the electron densities of structures for dose calculation from MRI scans. The widely published method is to create a synthetic CT scan (sCT)<sup>6</sup>. If the Hounsfield units of the synthetic CT scan are sufficiently similar to the physical CT scan then it is inferred that doses calculated on each scan will be similar and within clinically acceptable limits. It is difficult to assess from simply a Hounsfield unit comparison so doses calculated on each scan are usually compared.

Previous work by Dowling et al., (2015) has shown that the creation of sCT scans from MRI is a viable method for prostate treatment. Dowling's method uses a conventional T2-weighted scan sequence for the creation of the sCT scan<sup>6</sup>. This scan was then compared against an atlas or library of CT-MRI pairs and used deformable registration to create the sCT scan for the new MRI. Their methods are easy and practical to implement which makes it ideal for incorporating into radiation therapy planning. Dowling compared the similarity of the electron density information for the sCT scan against that of a CT scan of the same patient and reported good similarity (Figure 3). Results showed the mean error between the CT and sCT to be 0.6 +/- 14.7HU and the mean error within a single structure to be 40.5 +/- 8.2HU. They then copied the IMRT plan from the original CT scan over to the sCT scan and showed that with a 99.6% +/- 0.3% agreement, that there was little to no difference in the dosimetry between the plans (Figure 4)<sup>6</sup>.

Author: Laura O'Connor	Date Created: 22/03/2017
Reviewed by: Jarad Martin, Peter Greer, Joanne Smart, Jason Dowling	Review Date: 23/08/17
UNCONTROLLED WHEN PRINTED	



**Figure 3.**  
 Previous work in prostate planning<sup>6</sup>  
**A)** T2 MRI scan,  
**B)** Synthetic CT scan created from the acquired MRI  
**C)** Planning CT scan for the same patient,  
**D)** Difference B and C when overlaid – white is areas of difference, black is areas of no difference.



**Figure 4.**  
 Dosimetric comparison between sCT and CT in prostate planning.  
**A)** Original CT scan with dose plan overlaid,  
**B)** Estimate sCT for this patient,  
**C)** gamma map,  
**D)** Dose volume histogram results comparing OAR doses from sCT scan and CT scan<sup>6</sup>.

## 2.5 Applying this Method to Complex Pelvic Cases

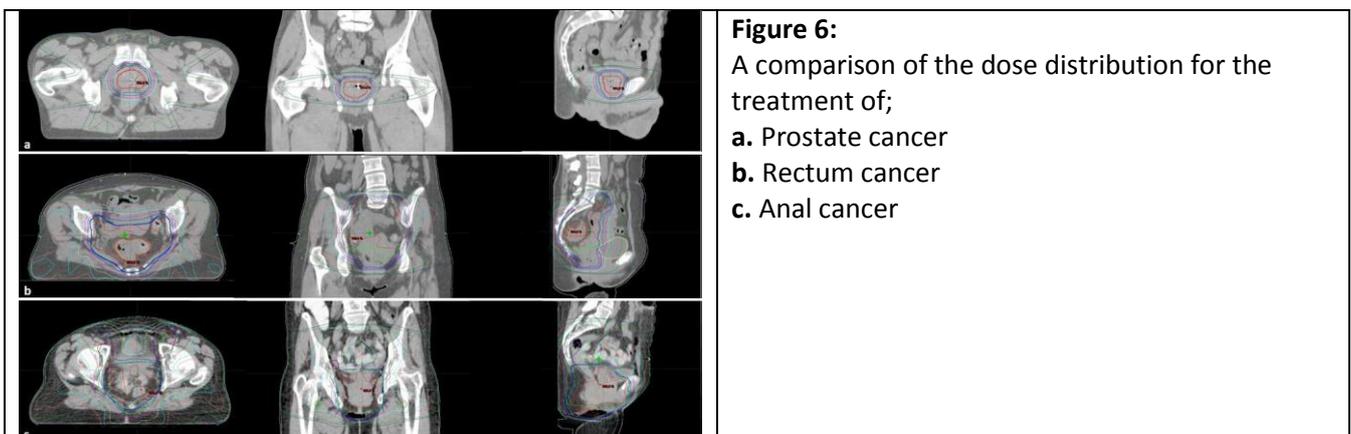
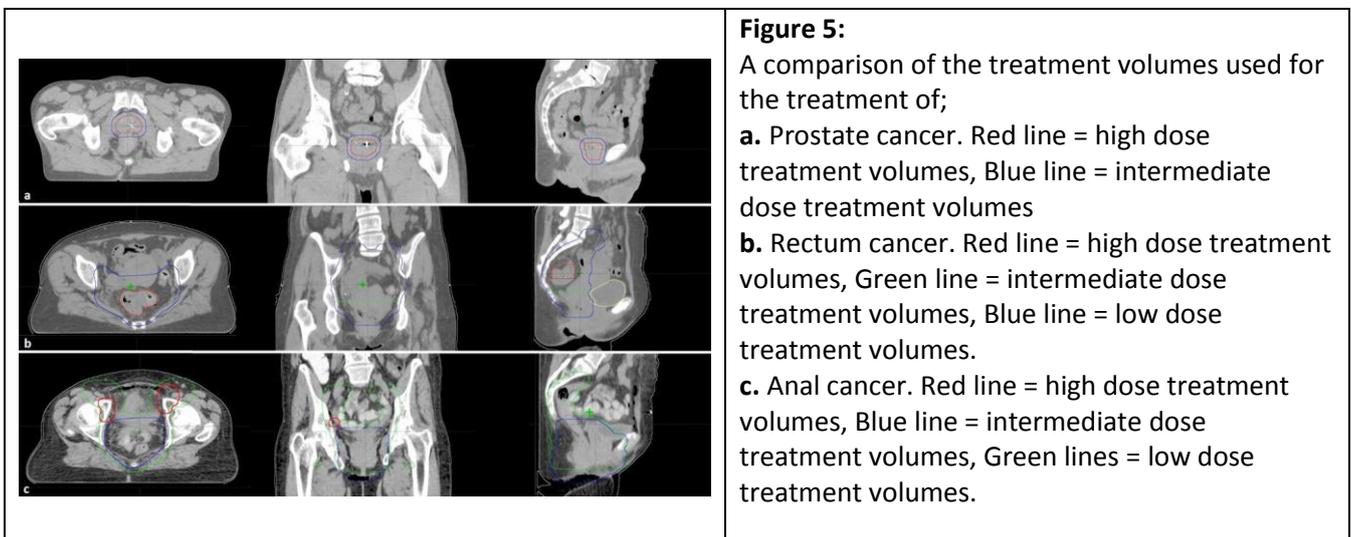
This method has proven to work for prostate cancer<sup>6</sup>; however, the treatment volumes for complex pelvic cancer are much more multifarious than in prostate cancer. The prostate is a spherical volume which means that the treatment is relatively simple and uniform. Rectal, anal and gynaecological treatments routinely involve treating the gross tumour volume, surrounding tissue deemed to be at high risk of tumour spread, the disease positive nodes and the surrounding local nodal volumes to a different radiation therapy prescription. The volumes for these patients are comparatively larger, irregular in shape and each are prescribed to a different dose level (Figure 5). This greatly increases the complexity of these treatments and the resulting dose distribution (Figure 6). The dose map (fluence) required for each beam is also more complex (Figure 7) as the fluence of each beam is aiming to wrap the high dose around the volumes of interest while avoiding the OARs close to the volume. Therefore, because of the increase in complexity of the rectum, anal canal and gynaecological plans compared to the prostate plans, there needs to be an investigation of the more complex dose distribution and fluence maps for these plans when they are applied to a sCT.

Another consideration for these treatment sites is that the anatomy is more variable from day-to-day. The effectiveness of the sCT method which uses library atlas scans registered to the new MRI scan will need to be

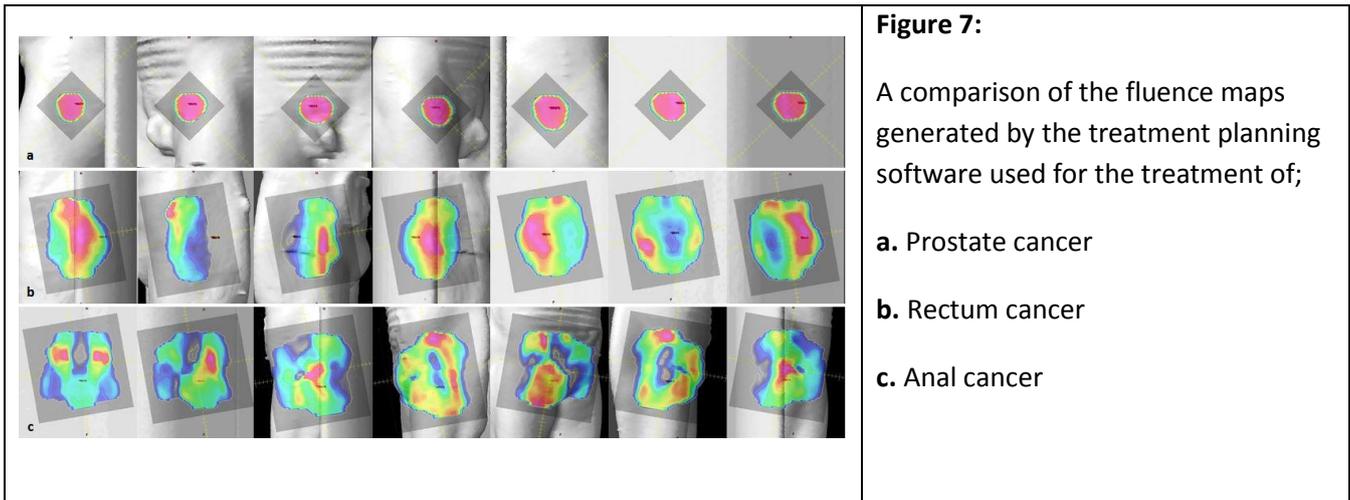
<b>Author:</b> Laura O'Connor	<b>Date Created:</b> 22/03/2017
<b>Reviewed by:</b> Jarad Martin, Peter Greer, Joanne Smart, Jason Dowling	<b>Review Date:</b> 23/08/17
<b>UNCONTROLLED WHEN PRINTED</b>	

investigated for a more variable anatomical site. This is because, if the new patient anatomy is sufficiently different from the atlas scans then the sCT dose planning accuracy will be lessened. The sensitivity of the method to consider and account for anatomical variations therefore must be determined.

In this project we propose to perform a retrospective feasibility study of MRI only planning for rectal, anal canal and gynaecological cancer radiation therapy. Planning MRIs will be taken with the patients in the treatment position and will be used retrospectively to create sCT scans to calculate a planned dose. Treatment accuracy and safety will be confirmed by comparing the dose calculation on the substitute CT with dose calculation on the standard CT scan. This study is a pilot study, therefore is not formally powered as a non-inferiority study. It is expected the mean dose difference between the CT and sCT to be 1%, inspection of the 95% confidence interval around the estimate of the mean dose difference will inform a larger trial regarding the potential non-inferiority of the new approach. Given this is a retrospective study, patients on this study will undergo the gold standard planning and treatment process i.e. The sCT will not be used to influence the planning of the participant's treatment.



Author: Laura O'Connor	Date Created: 22/03/2017
Reviewed by: Jarad Martin, Peter Greer, Joanne Smart, Jason Dowling	Review Date: 23/08/17
UNCONTROLLED WHEN PRINTED	



## Hypothesis

**A MRI only workflow for anal canal, gynaecological and rectal cancer radiation therapy planning is feasible using synthetic CT scans derived from MRI data.** We will calculate the difference in dose calculated on synthetic CT and actual CT for this patient group. If the mean dose difference is within 1% and the image guidance positioning using synthetic CT is within 1mm on average of CT, then we will accept the hypothesis.

## 2.6 Aims

This project aims to determine the feasibility of applying a previously developed method to create synthetic CT scans from pelvis MRI for complex pelvic cancer treatment planning. We will apply the same techniques as has been used for prostate MRI only planning, however we will determine if the more complex planning for rectal, anal canal and gynaecological patients is affected by the synthetic CT scans.

Specific Aims:

1. Acquire planning MRI and CT scans in treatment position. Create synthetic CT scans for abdomen/pelvic regions.
2. Evaluate the doses calculated on the synthetic CT scan and compare to the doses calculated on the patients CT scan.
3. Evaluate the suitability of the synthetic CT scan for treatment guidance DRR and CBCT generation
4. Evaluate the feasibility and reliability of using this method for the treatment of Rectal, Gynaecological and Anal canal treatments.

Author: Laura O'Connor	Date Created: 22/03/2017
Reviewed by: Jarad Martin, Peter Greer, Joanne Smart, Jason Dowling	Review Date: 23/08/17
UNCONTROLLED WHEN PRINTED	

## Study Design

This is a feasibility study to investigate if using synthetic CT scans of the pelvic region for MRI only radiation therapy planning of complex pelvic treatments, delivers the same results as a previous study into prostate treatment planning.

## Methods: Participants, Interventions, and Outcomes

### Study setting

The study will take place at the Calvary Mater Newcastle, Newcastle. The substitute CT scans will be created at CSIRO E-Health Research Centre, Brisbane using de-identified MRI scans. All institutions are within Australia.

### Participants

This is a single arm, single centre study to be performed at the Calvary Mater Newcastle requiring a 40 patient cohort (20 male and 20 female). The de-identified MRI scans will be sent to CSIRO E-Health Research Centre, Brisbane for the creation of the synthetic CT scans.

#### 2.6.1 Eligibility Criteria

1. >18 years of age
2. Patient able to provide informed consent
3. Histological diagnosis of a malignancy of the rectum, anal canal, cervix or endometrium
4. To be treated definitively with radical Radiotherapy +/- concurrent chemotherapy +/- surgery
5. Suitable for IMRT or VMAT planning

#### 2.6.2 Exclusion Criteria

1. ECOG performance status >1
2. Clinical evidence of distant metastatic disease
3. Women who are pregnant or lactating
4. Inability to have a MRI due to:
  - a. Implanted magnetic metal e.g. intraocular metal, aneurysm clip, or other metallic implant
  - b. Pacemaker/ implanted defibrillator
  - c. Extreme claustrophobia
5. Mental impairment/intellectual impairment in which the patient would have difficulty giving informed consent to the study
6. Bariatric patients (patients with a BMI > 30)

<b>Author:</b> Laura O'Connor	<b>Date Created:</b> 22/03/2017
<b>Reviewed by:</b> Jarad Martin, Peter Greer, Joanne Smart, Jason Dowling	<b>Review Date:</b> 23/08/17
<b>UNCONTROLLED WHEN PRINTED</b>	

## 2.7 Interventions

The participants will be required to undergo an additional planning MRI scan for this study. There is no additional cost to the participant for the MRI scan; the cost of the MRI scan will be covered by a Calvary Mater Newcastle research grant. There will be no change to the participant's treatment in this study – they will receive the gold standard of care and treatment as per departmental protocols. The MRI scan will be used for comparative purposes only.

### ***What is the “intervention?”***

The intervention involves an additional MRI scan being required for the study. This will require attendance at one MRI scan session of a half hour duration from the participant. This modification does not affect the gold standard of imaging the patients would otherwise receive. This MRI scan will be undertaken at the Diagnostic Imaging Department, Calvary Mater Newcastle, scheduled on the same day as the participants planning CT scan.

#### **2.7.1.1. Discontinuing the “intervention”**

n/a

## 2.8 Outcomes/Endpoints

### **2.8.1 Primary**

- To demonstrate the mean dosimetric agreement and 95% confidence interval between conventional CT and synthetic CT for radiotherapy treatment planning of cancers of the rectum, anal canal, endometrium and cervix.

### **2.8.2 Secondary**

- To demonstrate the Hounsfield Unit comparison of conventional CT and synthetic CT for complex pelvic cancers using mean absolute error
- To demonstrate the generation of digitally reconstructed radiographs (DRR's) from synthetic CT for on treatment guidance. A mock image guidance alignment will be performed using synthetic CT DRR based alignment and cone-beam CT based alignment. The differences in these measurements compared to the gold standard CT will be quantified.

### **2.8.3 Measurement variables and analysis metrics**

A Hounsfield unit comparison, DVH comparison and two-dimensional gamma analysis will be performed as part of the measurement and analysis. The analysis methods will be based on Dowling et al.<sup>6</sup> study comparisons of dose calculations on synthetic CT and conventional CT. These analytical methods have been justified by their

<b>Author:</b> Laura O'Connor	<b>Date Created:</b> 22/03/2017
<b>Reviewed by:</b> Jarad Martin, Peter Greer, Joanne Smart, Jason Dowling	<b>Review Date:</b> 23/08/17
<b>UNCONTROLLED WHEN PRINTED</b>	

wide use in other similar publications<sup>4, 7-11</sup>. These analysis metrics are described in greater detail in the previous section on Interventions and in more detail in the Methods section below.

#### 2.8.4 Harm outcomes

There are no specific harm outcomes for this study. IV contrast is **not** required for the MRI imaging. The MRI imaging is deemed as low to negligible risk; however, the standard risks associated with MRI do apply. These include patient claustrophobia and the risks associated with metal implants and implanted defibrillators/pacemakers. Patients will be screened for metal implants, pacemakers or defibrillators prior to the MRI using the standard MRI questionnaire form. Participants will be deemed ineligible for the study if they do have any of these devices or if it is deemed unsafe for them to have a MRI for any other reason. There are no specific harm outcomes for this study.

### 2.9 Participant timeline

Participants will attend for their routine CT simulation and then will proceed to have an additional MRI following this appointment, of a half hour duration. Patient's treatment start date will not be affected by this process.

### 2.10 Sample Size

The sample size will consist of 40 patients (20 male and 20 female patients) diagnosed with histologically confirmed malignancy of the rectum, anal canal, cervix or endometrium indicated for definitive radiotherapy, and who are eligible to undergo an MRI examination.

Prior experience in early phase development of the synthetic CT software suggests that a minimum sample of 20 participants is required to create an accurate sCT atlas. The contouring atlas which is used for this study to develop the synthetic CT scans cannot generalise between genders, therefore males and females would be required to be separated into 2 different groups. As 20 participants of each group will need to be recruited to generate a reliable sCT atlas, 40 patients will be recruited to the study; 20 male patients and 20 female patients. Assuming the dose difference at the representative voxel is 1.5% (based on content knowledge and prior experience), a sample of 20 participants, each with a CT and sCT, will enable estimation of the mean percentage dose difference and 95% confidence interval with a 0.7% (absolute) margin of error.

### 2.11 Recruitment

Participants will be recruited from the outpatient Radiation Oncology department at the Calvary Mater Newcastle. Potential patients will be screened by the research trial coordinators. Eligible patients will be introduced to the study by the treating Radiation Oncologist.

Informed consent will be obtained before patient is enrolled on the study. Information about the study will be discussed with prospective participants, who will be given time to consider the Patient Information and Consent

<b>Author:</b> Laura O'Connor	<b>Date Created:</b> 22/03/2017
<b>Reviewed by:</b> Jarad Martin, Peter Greer, Joanne Smart, Jason Dowling	<b>Review Date:</b> 23/08/17
<b>UNCONTROLLED WHEN PRINTED</b>	

Form (PICF). The Research Radiation Therapist will phone potential participants after the initial patient consultation and before their scheduled planning CT to review this information again along with the patient's interest in study participation to ensure they have fully comprehended the information provided.

Patients will be informed that their participation is voluntary and if they decline to be a part of the study, that their standard of treatment will not be affected. Participants will also be informed that they can withdraw from the study at any point if they wish to without explanation or any consequences.

Informed consent will be obtained by the Research Radiation Therapist. If the patient wishes to proceed with the study, eligibility will be confirmed and verbal consent will be obtained by phone. A MRI safety questionnaire will be completed over the phone in order for the MRI appointment to be made.

When the patient arrives for their planning CT scan, the Research Radiation Therapist will revise the study information with the patient to ensure that they are still willing to go ahead with the study. If the patient is still willing to participate in the study, the Research Radiation Therapist will obtain signed consent from the patient. Patients will be reminded that if they do not wish to go ahead with the study that no explanation is required and declining to take part in the study will not affect the standard treatment which they will receive. Any agreement will be voluntary, and free from coercion. Consent will be obtained by the Research Radiation Therapist.

## 3 Methods: Data Collection, management and analysis

### 3.1 Data Collection Methods

#### Conventional CT scanning

Participants will be simulated as per department protocol with a 2.5 mm trans-axial slice CT scan using either the Toshiba Aquillon or the GE LightSpeed CT scanners, using the inbuilt pelvic protocol (120kV or 135-140kV for larger patients). The anatomical scan levels will include the top of the L3 vertebra superiorly, inferiorly to include the upper 1/3<sup>rd</sup> of the femur. Patients are to be immobilised supine, using a custom vacbag for their legs and pelvic region, arms on chest with a comfortably full bladder. Patients will be tattooed as normal as per department protocol for pelvic patients with lateral tattoos and anterior tattoo for levelling, rotation and setup.

#### MRI Scanning

After CT-simulation, the patient is to proceed to MRI (on the same day, with as little time as possible between the CT and MRI scan sessions). All participants will have the RT planning position MRI scan at the Hunter New England Health Diagnostic Service using the Siemens 'Skyra' 3T scanner. The participant will be positioned **exactly** as they were for the planning CT scan on the RT CIVCO couch-top using the custom made vacbag created at the CT simulation and straightened using the LAP laser system and the levelling tattoos applied at the time of the planning CT. A radiation therapist will be in attendance at this session to ensure accurate setup.

Author: Laura O'Connor	Date Created: 22/03/2017
Reviewed by: Jarad Martin, Peter Greer, Joanne Smart, Jason Dowling	Review Date: 23/08/17
UNCONTROLLED WHEN PRINTED	

One 18-channel bodyflex surface coil will be placed over the pelvic region using a coil mounts supplied by CIVCO Medical Solutions. Scans will be acquired as per the department MRI pelvic protocol.

### Synthetic CT Generation

The MRI scans will be anonymised using Dicom+ and the study ID will be inserted into the DICOM header in place of the Patient MRN and Name. The anonymised data sets will then be uploaded to CSIRO secure Cloud Upload Site server for synthetic CT creation and analysis. Dr Jason Dowling will be notified of the upload via email ([Jason.Dowling@csiro.au](mailto:Jason.Dowling@csiro.au)). N4 bias correction will be used for MRI scans. The synthetic CT will be created using the same method as we have previously reported above. A Key matching the Patient MRN to the Study ID will be securely maintained by the Research Radiation Therapist. Following the return of the Synthetic CT from the CSIRO, the patient MRN and Name will be reinserted to the DICOM headers using the key.

### Import into Treatment Planning System

The planning CT, planning MRI and synthetic CT will be imported into the radiation therapy treatment planning system and fused using rigid registration. Other diagnostic imaging i.e. PET will then be fused to the sets as required. The radiation oncologist will then contour the patient as per department protocol.

### Radiation Oncologist contouring

As per department protocol, the radiation oncologist will delineate the following structures on the planning CT scan;

<b>3.1.1 Standard RO Structure Delineation</b>	
GTV NODES	PTV2
GTV PRIMARY	RO GENITALS
CTV NODES	RO SMALL BOWEL
CTV PRIMARY	RO BLADDER
CTV PRIMARY_ITV	RO RECTUM
PTV1	

The research radiation therapist will delineate the Bones on both the MRI and CT scan

### Treatment Planning

Participants on this study will have the same planning and treatment process as other patients – i.e. the sCT will be created for retrospective assessment and will not be used to influence the planning of the participant’s treatment. Participants may be planned using IMRT or VMAT for this study as is clinically appropriate. The Radiation Oncologist will approve the plan script electronically for treatment as per department procedure.

<b>Author:</b> Laura O’Connor	<b>Date Created:</b> 22/03/2017
<b>Reviewed by:</b> Jarad Martin, Peter Greer, Joanne Smart, Jason Dowling	<b>Review Date:</b> 23/08/17
<b>UNCONTROLLED WHEN PRINTED</b>	

Radiation therapists and medical physics staff will perform participant specific pre-treatment checks of the plan. Pre-treatment dosimetric measurement based checks must be performed.

### Synthetic CT evaluation

The Research Radiation Therapist (RRT) will be required to import the MRI scans, CT and synthetic CT scan and approved treatment plan into the Research Eclipse treatment planning system. The transfer will include the planned contours so that dose may be calculated on the synthetic CT.

The RRT will also produce digitally reconstructed radiographs (DRRs) for comparison if they were used for image guidance compared to those constructed from the standard planning CT.

Dose Calculation on synthetic CT: The original dose plan from the CT scan will then be copied across to the synthetic CT and re-calculated. This will then be compared to the dose calculated on the CT for the same beam arrangement. The dose at the International Commissioning on Radiation Units and Measurements (ICRU) point; a three dimensional Gamma comparison and a dose-volume histogram (DVH) parameters for the PTV and surrounding organs will be compared to quantify dose differences.

The Hounsfield unit comparison will be assessed by the mean absolute error in the patient's body contour and within corresponding structures such as: PTV, small bowel, bladder, rectum, and genitals.

Image Guidance Accuracy: Measurements of key image guidance features in the scans, ConeBeam CTs (CBCTs) and DRRs will be made referenced to isocentre. Mock image guidance alignment will be performed using synthetic CT DRR based alignment and cone-beam CT based alignment. The differences in these measurements compared to the gold standard CT will be quantified.

## 3.2 Data Management

Standard practices will be followed for clinical study data management. Participant MRI scans will be de-identified and then sent to the CSIRO Brisbane, via a secure cloud server, for synthetic CT creation. The synthetic CT scans will be sent back via the secure cloud server. The Research Radiation Therapist will be required to import the MRI scan, CT and synthetic CT scan into the Research Eclipse station. Files and data will be stored in compliance with hospital and department policy. Only staff listed in the study protocol will have access to trial information and data management. All data will be stored as a computer file on secure drives with access restricted to study staff.

## 3.3 Statistical Methods

There are no specific statistical methods in this study. Analysis of results will be performed using the same method in Dowling et al's (2015) study. A three dimensional gamma analysis will evaluate the dose-difference and distance-to-agreement with a global dose criterion of 2mm/2% (distance-to-agreement/dose-difference)

<b>Author:</b> Laura O'Connor	<b>Date Created:</b> 22/03/2017
<b>Reviewed by:</b> Jarad Martin, Peter Greer, Joanne Smart, Jason Dowling	<b>Review Date:</b> 23/08/17
<b>UNCONTROLLED WHEN PRINTED</b>	

and 1mm/1% using in-house MATLAB code. The mean dose difference at reference voxels will be compared between the CT and sCT scans. Dose within the PTV and dose within the entire body will be assessed. The dose distributions on the CT and sCT will also be compared using DVH parameters provided by the Eclipse planning system to assess doses to the PTV and contoured organs at risk. These will be assessed at specific points along the histogram for each structure. The mean difference and standard deviation will be recorded. The ICRU point dose difference will be determined by the change in monitor units between the two plans. The percentage difference will be recorded for each patient.

Feasibility of implementation of MRI-alone planning will be demonstrated if more than 90% of substitute CT patient plans are deemed acceptable for treatment given the above criteria. This allows for 4 out of 40 patient plans to be deemed unacceptable. The previous study by Dowling et al<sup>6</sup> determined that 100% of 39 patient plans would have met the equivalence criteria of this study.

## 4 Methods: Monitoring

---

### 4.1 Data Monitoring

Due to the nature of the study, specific data monitoring is not required for this study. This is a small workflow study where there is no experimental intervention designed to change participant outcomes to treatment.

### 4.2 Harms

There are no specific harm outcomes for this study.

## 5 Ethics and Dissemination

---

### 5.1 Research Ethic Approval

Research Ethics and governance approval and will be applied for through the Hunter New England Health HREC.

### 5.2 Informed Consent

Informed consent will be obtained by the Research Radiation Therapist

### 5.3 Confidentiality

Confidentiality will be maintained for participants as per hospital and department policy. The only information collected about the participants will be the scan data from the CT and MRI scans. Standard practices will be followed for clinical study data management. Participant MRI scans will be de-identified before being sent to the CSIRO Brisbane. Files and data will be stored in compliance with hospital and department policy. Only staff

<b>Author:</b> Laura O'Connor	<b>Date Created:</b> 22/03/2017
<b>Reviewed by:</b> Jarad Martin, Peter Greer, Joanne Smart, Jason Dowling	<b>Review Date:</b> 23/08/17
<b>UNCONTROLLED WHEN PRINTED</b>	

listed in the study protocol will have access to trial information and data management. All data will be stored as a computer file on secure drives with access restricted to study staff. In the dissemination of results, the result data will be pooled, no participants will be identifiable.

#### **5.4 Declaration of Interests**

N/A

#### **5.5 Access of Data**

Only staff listed in the study protocol will have access to trial information and data management. All data will be stored as a computer file on secure drives with access restricted to study staff. The data is owned and kept by the study management committee.

#### **5.6 Ancillary and Post Trial Care**

Participants will have access to regular avenues for compensation made available to all patients receiving radiation treatment within a public hospital

#### **5.7 Dissemination Policy**

It is intended that the results from the study will be published in a peer reviewed journal.

<b>Author: Laura O'Connor</b>	<b>Date Created: 22/03/2017</b>
<b>Reviewed by: Jarad Martin, Peter Greer, Joanne Smart, Jason Dowling</b>	<b>Review Date: 23/08/17</b>
<b>UNCONTROLLED WHEN PRINTED</b>	

## 6 References

1. Australian Government: Cancer Australia (2015). *Gynaecological Cancers*. Retrieved 15 March 2017 from, <https://canceraustralia.gov.au/affected-cancer/cancer-types/gynaecological-cancers>
2. Bowel Cancer Australia (2016a). *Treatment Options for Colon and Rectal Cancer*. Retrieved 19 July 2016 from, <https://www.bowelcanceraustralia.org/treatment>
3. Tobias JS. The role of radiotherapy in the management of cancer – an overview. *Ann Acad Med Singapore* 1996;25(3):371-379
4. Kim J, Glide-Hurst C, Doemer A, et al. Implementation of a novel algorithm for generating synthetic CT images from magnetic resonance imaging data sets for prostate cancer radiation therapy. *Int J Radiat Oncol Biol Phys* 2015;91:39-47
5. The Royal Australian and New Zealand College of Radiologists (2014). *Imaging in Radiation Oncology – A RANZCR Consensus White Paper*. Retrieved October 4, 2016 from, <http://www.ranzcr.edu.au/documents-download/document-library-2/document-library-4/3300-imaging-in-radiation-oncology-white-paper>
6. Dowling, J. A., Sun, J., Pichler, P., Rivest-Henault, D., Ghose, S., Richardson, H., ... Greer, P. (2015). Automatic Substitute Computed Tomography Generation and Contouring for Magnetic Resonance Imaging (MRI) – Alone External Beam Radiation Therapy From standard MRI Sequences. *Int J Radiation Oncol Biol Phys*. 93(5), 1144-1153
7. Lee YK, Bollet M, Charles-Edwards G, et al. Radiotherapy treatment planning of prostate cancer using magnetic resonance imaging alone. *Radiother Oncol* 2003;66:203-216
8. Chen LL, Price RA, Wang L, et al. MRI-based treatment planning for radiotherapy: Dosimetric Verification for prostate IMRT. *Int J Radiat Oncol Biol Phys* 2004;60:636-647
9. Guerreiro F, Burgos N, Dunlop A, et al. Evaluation of a multi-atlas CT synthesis approach for MRI-only radiotherapy treatment planning. *Phys Med* 2017;35:7-17
10. Wang C, Chao M, Lee L, et al. MRI-based treatment planning with electron density information mapped from CT images: A preliminary study. *Technol Cancer Res Treat* 2008;7:341-348
11. Stanescu T, Jans HS, Pervez N, et al. A study on the magnetic resonance imaging (MRI)-based radiation treatment planning of intracranial lesions. *Phys Med Biol* 2008;53:3579-3593
12. Kadam, P., & Bhalerao S. (2010) Sample Size Calculation. *Int J Ayurveda Res*. 1(1), 55-57

Author: Laura O'Connor	Date Created: 22/03/2017
Reviewed by: Jarad Martin, Peter Greer, Joanne Smart, Jason Dowling	Review Date: 23/08/17
UNCONTROLLED WHEN PRINTED	