Full title: **Evaluation of hypofractionated adaptive radiotherapy using the MR Linac in localised pancreatic cancer**

Short title: **EMERALD - Pancreas**

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## PROTOCOL SYNOPSIS

An MR Linac combines two technologies – a magnetic resonance imaging (MRI) scanner and a conventional radiotherapy treatment machine (also known as a linear accelerator - Linac). Having radiotherapy (RT) on an MR Linac allows high quality MR images to be taken daily before treatment and while the treatment is delivered with associated adaptation of the radiotherapy treatment- MR guided adaptive RT.

The optimal RT dose and schedule to treat pancreatic cancer is not known and doses have been limited by the need to keep the dose to normal surrounding tissues within accepted limits. Audit data has shown that when treatment is delivered on an MR Linac the tumour is targeted more effectively and normal tissues can be avoided. There is therefore the potential to safely deliver higher doses whilst keeping the dose to normal tissues within accepted limits. In this study we will evaluate whether increased RT doses and treatment over fewer days can be safely delivered to patients with pancreatic cancer on an MR Linac and whether this will improve the benefit of MR Linac treatment further.

This study will also look at whether there are any changes in the tumours and normal tissues over the course of RT that can be seen on the MR images taken by the MR Linac, with the aim to see if we can find indicators from the imaging which may in the future enable us to plan treatment more individually.

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| Short Title: | EMERALD-Pancreas |
| Primary Objective: | To establish the safety of MR-guided hypofractionation SBRT in localised pancreatic cancer |
| Secondary Objectives: | 1) Efficacy of MRgRT:<br>o Overall survival and Progression Free survival<br>o Local control rate<br>o Overall control rate<br>o Resection rates (including Resection margin status and pathological response)<br>2) Long term toxicity rates.<br>3) Freedom from second line chemotherapy |
| Tertiary/Exploratory Objectives: | To identify a biomarker derived from imaging analysis and other associated clinical and pathological data which predicts outcome from RT<br>To evaluate any change in immune status during or following SABR. |
| Primary Endpoint: | Dose Limiting Toxicity (DLT) within 3 months from start of MRgRT– defined as:<br>• Grade 3 upper gastro-intestinal bleeding<br>• Gastro-intestinal fistula (any grade)<br>• Grade 4 nausea/vomiting uncontrolled despite optimum anti-emetics<br>• Grade 4 pancreatitis not stent related<br>• Vascular events (where these are not considered to be tumour related) |
| Secondary Endpoints: | • Efficacy of MRgRT:<br>o Overall survival and Progression Free survival;<br>o Freedom from local progression<br>o Freedom from metastatic progression<br>o Definitive resection rate; For those undergoing surgery: R0/R1/R2 resection margin rates; For those undergoing surgery: Rate of pathological complete response<br>• Long term toxicity rates (only those specifically related to SBRT).<br>o All Grade 3+ toxicities to 12 weeks from start of MRgRT<br>o Any late GI AE > grade 2 (CTC v5) after 12 weeks from start of MRgRT.<br>• Freedom from further line chemotherapy<br>o Time from start of MRgRT to re-start of further chemotherapy |
| Exploratory Endpoint: | Imaging assessments |
| Other investigations: | Additional 0.35T MR imaging post fractions |
| Study Design: | Dose safety study (dose levels 50Gy in 5 fractions, 39 in 3 fractions, 25 Gy in 1 fraction) |
| Patient Numbers: | Maximum 60 patients. |
| Target Population: | Locally advanced pancreatic cancer |

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| | Resectable or borderline resectable disease where surgery is not feasible due to medical co-morbidities/patient choice.<br>Locally recurrent pancreatic cancer |
| Trial Intervention: | 5, 3 or 1-fraction MR Guided stereotactic radiotherapy over 1-3 weeks |
| Duration on study: | Up to 24 months from patient starting radiotherapy.<br>N.B. 12 months is planned for the recruitment period, however depending on the speed of recruitment, recruitment may be extended into the 12-month follow-up period. Most participants follow-up will be less than 24 months. All participants will be followed for at least 3 months and to the maximum time until study closure. |
| Study Procedures and frequency: | See over for assessment flowchart |
| Patient care post-trial: | As per routine clinical practice standard care |
| No. of Study Site(s) | 1 UK centres (Oxford University Hospital NHS Foundation Trust) |

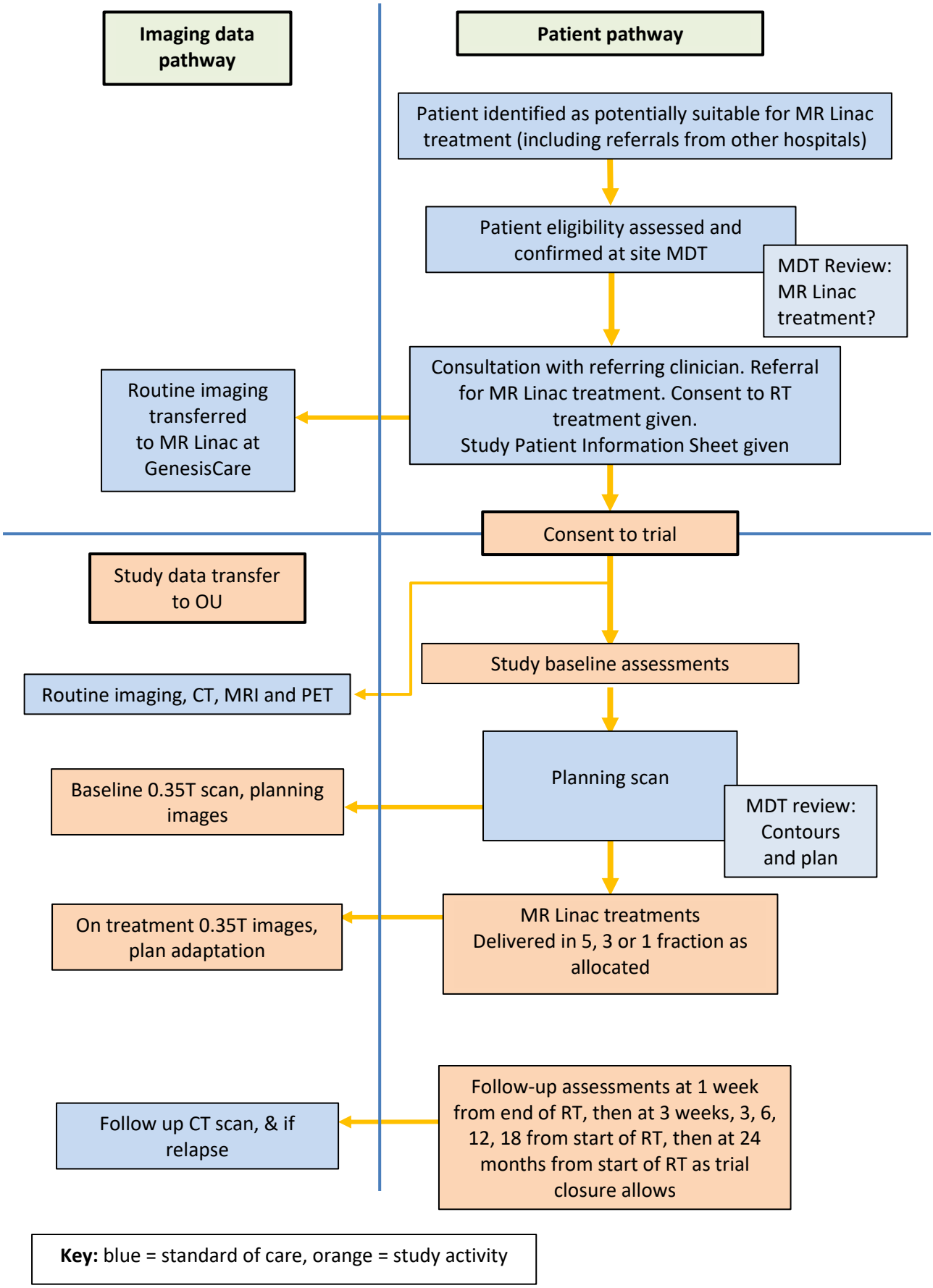
**SCHEDULE OF ASSESSMENTS**

| **Procedure** *(grey shading denotes SoC activities)* | **Pre-screening** Within 3 months of RT #1 | **Screening & baseline** Within 28 Days of planning scan | **Planning scan visit** | **RT fraction[13]** | | | | | **Post radiotherapy** | | | | | | | **Progress-ion** (if applicable) | **Early Withdra-wal** (if applicable) | **End of study[18] (+/-1 months)** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | **#1** | **#2** | **#3** | **#4** | **#5** | **+1 weeks[15] (+/- 4 days)** | **3 weeks[16] (+/- 1 wk)** | **6 weeks[16] (+/- 2 wks)** | **3 months[16] (+2 wks)** | **6 months[16] (+/- 1 mon)** | **12 months[16] (+/- 1 mon)** | **18 months[16] (+/- 1 mon)** | | | |
| **CT Scan TAP [1]** | X | | | | | | | | | | | X | X | X | | X | | |
| **Informed consent [2]** | | X | | | | | | | | | | | | | | | | |
| **Demographics[3]** | | X | | | | | | | | | | | | | | | | |
| **Baseline sign & symptoms[4]** | | X | | | | | | | | | | | | | | | | |
| **Medical history** | | X | | | | | | | | | | | | | | | | |
| **Haematology[5]** | | X | | | | | | | | | | X | | | | | | |
| **Biochemistry[6,7]** | | X | | | | | | | | | | X | | | | | | |
| **Ca19.9 tumour marker** | | X | | | | | | | | | | X | | | | | | |
| **Urine pregnancy test (WOCBP only)** | | X | | | | | | | | | | | | | | | | |
| **Clinical review & disease assessment [8]** | | X | | | | | | | X | X | X | X | X | X | X | | X | |
| **Performance status (ECOG)** | | X | | X[14] | | | | | X | | X | X | X | X | X | | | |
| **AE review [9]** | | | X[20] | X | X | X | X | X | X | X | X | X | X | X | X | | X | X |
| **DLT review** | | | | X | X | X | X | X | X | X | X | X | | | | | X[17] | |
| **Late-onset severe toxicities review** | | | | | | | | | | | | | X | X | X | | X[19] | X |
| **Planning scan (0.35T MRI) [10]** | | | X | | | | | | | | | | | | | | | |
| **MR Linac treatment [11]** | | | | X | X | X | X | X | | | | | | | | | | |
| **Data capture: PFS, survival status, resection status, restart of chemotherapy & locoregional failure[12]** | | | | | | | | | | | | X | X | X [18] | X | X | X [18] | X [18] |
| **Reason for withdrawal** | | | | | | | | | | | | | | | | | X | |

1. Standard of care diagnostic CT and optional MRI are used as baseline imaging and whole-body PET-CT if performed in routine care. Further CT scans (& MRI, PET-CT where applicable) at 3, 6 & 12 months follow-up and if relapse/progression occurs are also standard of care. Scans and clinical report to be pseudonymised with trial subject ID and transferred to OU. Scan images and report need to be transferred to the OU if scan carried out at another trust.
2. See section 4.5 for further information on informed consent process.

3. Demographic details to include age and sex
4. Baseline Sign and Symptoms: provide date of onset, event diagnosis (if known) or sign/symptom, severity, time course. Terms should be specific medical terms according to NCI CTCAE version 5. Please avoid using abbreviations, combined terms e.g. nausea and vomiting and ambiguous terms e.g. deranged, abnormal.
5. Haematology: Full Blood Count.
6. eGFR at baseline only.
7. Biochemistry: sodium, potassium, urea and electrolytes, creatinine, ALT or AST, Bilirubin, Albumin, alkaline phosphatase.
8. As considered appropriate by clinician. In follow-up this should include disease assessment for progression
9. AE assessment may be undertaken face to face, by telephone or audio/video call through the internet.
10. The planning scan is required as a routine part of clinical care, for the study an additional set of research images may be acquired during the planning scan.
11. MR Linac treatment will be given in 5, 3 or 1 fractions as per dose selection process detailed in section 10.0 & 10.1.
12. For participants who have not reached 24 months follow-up at study closure this data will be collected at an earlier timepoint, at least 3 months after start of RT and as close as possible to study closure.
13. Fractions may be missed/delayed at Investigators' discretion
14. ECOG status prior to fraction 1.
15. From completion of radiotherapy
16. From start of radiotherapy
17. If early withdrawal is <u>within</u> 3-month DLT collection window
18. Evaluations to be completed at end of study, 24 months (from RT Fraction #1) follow-up or death
19. If early withdrawal is <u>after</u> 3-month DLT Collection window.
20. The AE Review at the Planning Scan Visit can be performed with the RT Fraction #1 AE review, as long as the review includes AE assessment from the Planning Scan Visit date.

**STUDY PATIENT FLOW CHART**




**Key:** blue = standard of care, orange = study activity

## ABBREVIATIONS

| | |
|---|---|
| 0.35 T, 1.5 T, 3 T | 0.35, 1.5, 3 Tesla (magnetic field strength) |
| AE | Adverse Event |
| ADC | Apparent Diffusion Coefficient |
| CA | Coeliac axis |
| CAP | Compassionate Access Programme |
| CBCT | Cone Beam CT |
| CERR | Computational Environment for Radiotherapy Research |
| CFRT | Conventionally fractionated radiation therapy |
| CI | Chief Investigator |
| CRF | Case Report Form |
| CRT | Chemotherapy and RT |
| CTCAE | Common Terminology Criteria for Adverse Events |
| CT TAP | Computerised Tomography Thorax Abdomen and Pelvis |
| CtE | Commissioning through Evaluation |
| CTV | Clinical Target Volume |
| DART | Daily Adaptive RT |
| DIB | Delta Image-derived Biomarker |
| DICOM | Digital Images and Communications in Medicine |
| DLT | Dose limiting toxicity |
| DWI | Diffusion Weighted Imaging |
| ECOG | Eastern Cooperative Oncology Group |
| FBC | Full Blood Count |
| GCP | Good Clinical Practice |
| GTV | Gross Tumour Volume |
| HCC | Hepatocellular Carcinoma |
| IB | Image-derived Biomarker |
| ICF | Informed Consent Form |
| IGRT | Image-guided radiation therapy |
| ISF | Investigator Site File |
| LAPC | Locally advanced pancreatic cancer LAPC. |
| LANPC | Locally advanced non-metastatic pancreatic carcinoma |
| LARC | Locally Advanced Rectal Cancer |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MR(I) | Magnetic Resonance (Imaging) |
| MRLinac | Viewray MRIdian MR Linac (in this protocol) |
| MRgRT | Magnetic Resonance guided RT |
| MTD | Maximum Tolerated Dose |
| NCCN | National Comprehensive Cancer Network |
| OAR | Organs at risk |
| OART | Online Adaptive RT |
| OCTO | Oncology Clinical Trials Office |
| OCTRU | Oxford Clinical Trials Research Unit |
| OS | Overall Survival |
| OU | University of Oxford |
| PFS | Progression Free Survival |
| PI | Principal Investigator |
| PIS | Patient information sheet |
| PROMS | Patient reported outcome measures |
| PTV | Planned Target Volume |
| QA | Quality Assurance |
| QC | Quality Control |
| QMR(I) | Quantitative Magnetic Resonance (Imaging) |
| RTQA | Radiotherapy trial Quality Assurance (RTQA) |
| REC | Research Ethics Committee |
| RIOC | Radiotherapy and Imaging Oversight Committee |

| | |
|---|---|
| RoI | Region of Interest |
| RT | Radiotherapy |
| SABR/ SBRT | Stereotactic (ablative) body radiotherapy |
| SMA | Superior mesenteric artery |
| SMV | Superior mesenteric vein |
| SOP | Standard Operating Procedure |
| SRC | Safety Review Committee |
| SUSAR | Suspected Unexpected Serious Adverse Reaction |
| TMF | Trial Master File |
| TMG | Trial Management Group |
| TMZ | Temozolomide |
| TSC | Trial Steering Committee |
| WOCBP | Woman of child bearing potential |

# 1 INTRODUCTION

## 1.1 Background

Outcome of patients with pancreatic cancer is poor. In the UK, approximately 10,000 cases are diagnosed each year with approximately 8000 deaths per year (1). Surgery offers the best chance of cure, however only ~20% of patients are operable at diagnosis. 30-40% have locally advanced non-metastatic pancreatic carcinoma [LANPC] and another 40-50% have metastatic disease. The NCCN defines LANPC as tumour encasing the superior mesenteric artery (SMA) or coeliac axis (CA) by >180° the tumour or involvement of the CA and aorta. In addition, unreconstructable superior mesenteric vein (SMV) or portal vein (PV) due to tumour involvement or occlusion would deem the tumour unresectable(2).

The optimum treatment of patients with LANPC is unclear. Historically, these patients are managed similarly to patients with metastatic disease under the premise that this is largely a systemic disease(3). However, tumour downstaging to facilitate complete resection (4) and improving local control is likely to become more relevant in the face of improved systemic treatment. Although the role of RT is debated in pancreatic cancer, one randomized study of chemotherapy with/without consolidation chemoradiotherapy (54Gy/30 fractions) showed decrease in local progression (32% vs 46%, p=0.03) and delay in onset of second line chemotherapy (5). More recently, Stereotactic body radiation therapy (SBRT) where an ablative dose of RT is delivered to a small volume in 1-5 fractions, have been shown to achieve local control rates as high as 80-100% (see Table 1), compared to about 50% reported in CRT trials. Initial SBRT experiences for treatment of locally advanced pancreatic cancer with ablative doses of radiation had reported high rates of toxicity, particularly with regimens delivered in less than 5 fractions (Table 2).
5-fraction SBRT regimens demonstrate low toxicity, are more widely used, have been recently been commissioned by NHS England, and are rapidly replacing conventional CRT as the preferred mode for consolidation therapy following 3-6 months of induction chemotherapy (6). Although a 5-fraction RT is more attractive than a 25-fraction treatment and spares the toxicity of concomitant chemotherapy, SBRT is not without side effects. Serious toxicity (grade 3+) including gastro-intestinal toxicity (bleeding/ulceration/fistulation) is reported in ~10% of patients.

There have been a number of meta-analyses looking at patient outcomes with SBRT. A recently published meta-analysis including 1147 patients across 21 studies comparing conventionally fractionated radiation therapy (CFRT) versus SBRT in locally advanced pancreatic cancer showed SBRT statistically improved 2-year OS with decreased acute G3/4 toxicities(7). The meta-analysis included retrospective, phase II/III studies published between 2002 & 2014. The random effects estimate for 2-year OS was 26.9% (95%CI, 20.6%-33.6%) for SBRT vs 13.7% (95%CI, 8.9-19.3%) for CFRT. The most common dose for SBRT was 30Gy in 5 fractions ($BED_{10}$ = 60Gy). The random effects estimate for grade3/4 toxicity was 5.6% (95%CI, 0.0%-20%) for SBRT vs 37.7% (95% CI, 24.0-% -52.5%) for CFRT. The majority of patients received SBRT using CBCT image-guidance and fiducials. Petrelli et al, assessed the efficacy of SBRT for patients with locally advanced pancreatic cancer in 1009 patients in 19 published studies and found the pooled 1-year survival was 51.6% (8). The local control rate following SBRT at 1 year follow-up was 72.3% (95%CI, 58.5%-79%). Overall, the rate of acute severe toxicity ranged from 0% to 36% with only three studies showing grade ≥3 acute toxicity of more than 10%. The incidence of late grade ≥3 did not exceed 11% in the included studies.

However, further hypofractionation (1-3 fractions) using conventional CT-based SBRT has resulted in higher toxicity in the pancreas (see Table 2)(9, Didolkar, 2010 #4, 10). In a retrospective review, Didolkar et al, reported acute Grade 3 and above toxicities of 22.3% (10). Patients received prescribed doses of 30 to 50Gy in 3-5 fractions delivered with the

CyberKnife system. A large proportion of these patients had prior conventional radiotherapy. Furthermore, toxicities appeared to be lower in patients treated in the later years. Hoyer et al, conducted a phase II trial delivering 45Gy in 3 fractions using stereotactic body frame (9). They reported grade 3 and above acute and late toxicities of 78 and 33%. This may be a consequence of the large margins used for generating the planning target volume (PTV). Similarly, Liauw et al reported up to 27% grade 3 and above late toxicities following 3-fraction SBRT(11). However, no motion management was employed and large margins were used to generate a PTV. Therefore it is accepted that safe delivery of further hypofractionation (1-3 fractions) requires greater precision in technical radiotherapy delivery to allow more accurate tumour targeting, organ at risk (OAR) sparing and motion management that is currently available on CT-based SBRT platforms

### 1.2 Pancreas MRgRT

Although significant advances have been made in IGRT, the current method for ensuring highly-conformal dose delivery and tumour localisation is limited, especially in pancreatic cancer.

The challenge in delivering highly conformal RT in pancreatic cancer are:

1. Poor tumour and organ at risk localisation with CT imaging for treatment setup
2. Intra- and inter-fraction tumour and OAR motion

In conventional RT, treatment is planned using the best available imaging data from CT, PET-CT and MRI scans taken before treatment starts, and a single optimised treatment plan is prepared and this treatment is delivered each day during treatment. The position of the tumour is checked each day from surface markings and from cone beam CT. Various devices are in use to minimise tumour movement. However, involuntary movements continually occur which alter both the position of the tumour and the normal tissues around the tumour. Within the abdominal cavity, the bowel is constantly moving due to peristalsis and those areas of the bowel (small bowel and the fully peritonealised colon) may be highly mobile. Organs below and above the diaphragm move significantly with breathing. In addition to the challenges of tumour movement, image-guided RT (IGRT) based on cone-beam Computed Tomography (CT) imaging produces poor quality images for set-up due to poor soft tissue contrast (12).

Adaptive RT uses precise imaging to adapt the anatomical distribution of the RT dose from day to day during RT by adaptive replanning and also during delivery of the RT by gating. Adaptive radiotherapy using Magnetic Resonance Imaging (MRI) addresses both of these challenges directly as MR, as well as being the most versatile modality in terms of tissue visualisation and tumour identification in the upper abdomen, can provide real-time imaging of the tumour region of interest (RoI). Adaptive RT using MR imaging is achieved through the integration of RT and MRI devices into a single treatment platform called the MR Linac (13). The MR Linac platform to be used for this trial is a Viewray MRIdian MR Linac system and incorporates a 0.35T scanner (14-16).

The MR Linac provides an opportunity to improve dose distribution through superior soft-tissue definition without the need for fiducials, online adaptive planning, real-time soft-tissue tracking and gated delivery within an acceptable timescale. A number of planning and clinical studies have now shown that dose escalation while adhering to OAR constraints is possible with an MR linac(14, 16).

In a phase 1 trial of online adaptive RT using the ViewRay system, it was possible to identify and avoid unplanned overdose to organs at risk due to inter-fraction movement which occurred in 63% of fractions (12). In addition, it is possible to turn off (gate) the RT beam if necessary (e.g. if the tumour moves partially out of field) thereby avoiding under-dosing the tumour and delivering unnecessary dose to normal tissues due to intra-fraction movement (16). Online adaptive plans were created at the time of treatment for 81/97 fractions, due to initial plan violation of OAR constraints (61/97) or observed opportunity for PTV dose escalation (20/97). Plan adaptation increased PTV coverage in 64/97 fractions. No grade 3 or greater toxicities were observed suggesting that this detailed process to minimise dose to normal tissues is beneficial (12). MRgRT therefore offers significant potential for improved local disease control and longer-term treatment outcomes with reduced toxicity. Henke et al phase 1 trial failed to meet its primary endpoint of feasibility which was that >75% of fractions would be delivered in <80 minutes (12). The median duration of treatment was 79 mins/fraction but despite this, all treatments were delivered in full. Feasibility of treatment delivery within a time scale that is tolerable by the patients has already been demonstrated in the pretrial use of the MR Linac. Our median vault time for complex breath-hold treatment delivery in the first 4 months of our clinical service is 82 minutes (range 60-125 minutes).

There are clear dosimetric advantages and increasing evidence that MR-guided SBRT can improve outcomes in pancreatic cancer both from published data as well as local experience. Dosimetric analysis of online adaptive radiotherapy using the MR linac of our first 10 patients with locally advanced pancreatic cancer would support this toxicity finding; non-adaptive small volume critical OAR dose were shown to exceed adaptive doses to such a degree it would suggest that dose escalated adaptive radiotherapy would still maintain a significant safety advantage over non-dose escalated non-adaptive radiotherapy in pancreatic cancer, see Appendix 4 Dosimetry analysis). Volume of GI tract receiving a dose of 36Gy, seen as an indicative dose level for risk of grade 3 toxicity, or greater was a median of 0.00cc (0.00-0.1cc) for adaptive radiotherapy and 0.33 cc (0.00-12.7cc) for non-adaptive radiotherapy $p<0.05$. Sparing of GI tract was achieved without compromise of PTV dose coverage compared to baseline planning; with baseline plan PTV dose to 70% or more of PTV a median of 43.3Gy (42.5-45.3Gy) and adaptive fraction a median of 42.8Gy (40.5-45.4), $p>0.1$.

Our current clinical experience delivering SABR to pancreatic cancer under the Compassionate Access Programme (CAP) with GenesisCare on the MRLinac showed daily adaptive radiotherapy is feasible with acceptable acute grade 3+ toxicity rates of 10% (abstracts submitted to SABR Consortium 21 and ESTRO 22). The analysis included a total of 50 patients. The most common (46/50, 92%) prescription dose was 40 Gy in 5 fractions on alternate days. Median GTV volume was 49.6 cc (min 12.7 cc, max 273.1 cc). Forty-nine patients completed treatment. For baseline treatment plans, median target coverage was 77.9% (minimum 52.4%, maximum 95.0%) with no violations of mandatory OAR dose constraints (median OAR V36 = 0.0 cc). Predicted (i.e.non-adaptive) treatment plans showed increased doses to critical OARs (median OAR V36 = 0.6 cc, V33 = 1.2 cc). Using adaptive MRgRT, the re-optimised treatment plans showed no violations of mandatory OAR dose constraints (median OAR V36 = 0.0 cc, V33 = 0.01 cc) whilst maintaining target coverage (median 75.5%, min 48.5%, maximum 98.9%).

A retrospective analysis of 42 locally advanced pancreatic cancer patients treated by MR-guided adaptive RT at four institutions (UCLA, Los Angeles, CA, University of Wisconsin, VUmc, Amsterdam, and Washington University, St. Louis,) demonstrated that high-dose SBRT or hypofractionated radiation therapy delivered using daily adaptive dose planning has the potential to further improve overall survival (17) . A control group of 19 patients treated to more conventional radiation doses without frequent dose adaptation showed a median survival of 14.8 months, while patients treated to high radiation doses (n=23, maximum BED10 of >90 Gy) under daily or almost daily adaptive re-planning had an estimated median survival of 27.8 months (p=0.005). Interestingly, increased radiation dose delivery using daily dose adaptation was correlated with less grade 3 toxicity (0% in the high dose group vs 15.8% in patients treated to lower radiation doses without dose adaptation). Hall et al, summarised the current published experience for MRgRT in pancreatic cancer and found local control rates of between 77-88% at 1 year with toxicity rates of less than 10% (n=141 from 6 studies mostly retrospective) (18). The dose prescription range from 35-50Gy in 5 fractions. More recently, investigators at MCI (Miami, FL) retrospectively analysed 50 pancreatic cancer patients with 50Gy in 5 fraction using online daily adaptation on the ViewRay MRlinac and found 1-yr, and 2-yr estimated local control were 97.8%, and 88.9%, respectively. Median survival was 21 months (1 and 2-year OS 87.9% and 50%) (ESTRO 2021) (19). Acute and late grade 3+ toxicity rates were 2% and 10%, respectively.

Our in-silico planning study shows that three and single-fraction pancreas SBRT plans could be generated while meeting organ dose constraints and delivering a meaningful dose to the target. Furthermore, treatments could be delivered within a reasonable timeframe (see appendix 5, abstract submitted to ESTRO 22). Patients included in the study were from the CAP cohort (n=8, median GTV 41.35cc, (range 15.9-64.4). The median PTV V100 coverage for 39Gy/3# and 25Gy/1# was 75.7% (60.6-91.6%) and 66.1 (60.1-84.2%) respectively. The median treatment delivery times for 15.2min (12.5-21.7min) and 21.0min (15.9-33.2min) for 39Gy/3# and 25Gy/1# respectively.

Based on this prior data, we now plan to evaluate whether we can safely deliver 3 fraction and single fraction SABR to the pancreas using fully adaptive radiotherapy on the Viewray MRLinac, MRiDian. Shorter fractionation schedules are more convenient for patients and increase access to and cost-effectiveness of the scarce and expensive resource of an MR Linac. Being able to achieve high rates of local control of the primary tumour with minimal side effects and very limited impact on patient lives would be a great advantage for patients. It will also enable greater access for systemic therapies, including conventional chemotherapy and novel immunotherapies, to develop more effective long term control regimens to combat this highly aggressive disease. EMERALD-Pancreas is a phase I study whereby we wish to demonstrate that ablative doses of SBRT (higher dose 5-fraction SBRT, 3-fraction SBRT and single-fraction SBRT) can be delivered safely.

SABR is postulated to activate the immune system through release of tumour-associated antigens and activation of dendritic cell activation within the tumour microenvironment. This results in tumour-specific T cell activation and proliferation. Furthermore, radiation could lead to tumour lymphocyte infiltration by normalising vasculature and increasing expression of endothelial adhesion molecules. Optimisation of radiotherapy fractionation and addition of immunotherapy could improve outcome of patients with locally advanced pancreatic cancer (LAPC). The optimal fractionation for inducing and stimulating the immune system against pancreatic cancer is unknown.

**Imaging Research on the MR Linac**

Imaging with MR protocols suitably adapted to the MR Linac system can be used to extract Image-derived Biomarkers (IBs) that may aid in predicting the efficacy of the patient's current RT treatment plan. Such IBs may take the form of modality-specific quantities, such as tumour T1 or T2* values from conventional MRI or the Apparent Diffusion Coefficient (ADC) from Diffusion Weighted Imaging (DWI); or they may be features derived from a radiomics-based analysis of the image itself. Furthermore, this imaging window is available at each RT session, i.e. daily in most cases – which means that the rate of change of the IBs, or Delta-Image-derived Biomarkers (DIBs) – can be tracked over time. This high frequency, patient-specific longitudinal imaging data would add another dimension to the IDB's potential diagnostic and prognostic power, and aid clinicians as they leverage MRgRT as part of the personalised medicine paradigm. In this study we will collect imaging data and transfer it to a separate Research Imaging Database which will be separately funded and have its own IRAS approval.

**Table1. Borderline resectable and locally advanced pancreatic cancer studies (outcomes)**

| Study | Resectability | no | Study type | RT technique | Dose fractionation | BED (Gy) | Median OS (month) | Median PFS (mon) | 12 month OS | 12 month PFS | LC |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Chuong (20) | BRPC | 30 | Retro | Fiducials | 5-6 Gy x 5F | 37.5-48 | 20 | 14.9 | 91% | 61% | NR |
| Chuong (21) | BRPC | 57 | Retro | Fiducials | 5-6 Gy x 5F | 37.5-48 | 16.4 | 9.7 | 72.2% | 42.8% | 81% (12 non unresectable) |
| | LA | 16 | | | | | 15 | 9.8 | 68.1% | 41% | |
| Mahadevan (22) | LA | 39 | Retro | Cyberknife | 8-10Gy x 3F | 43.2-60 | 20 | 15 | NR | NR | 85% (21 mon) |
| Mahadevan (23) | LA | 36 | Retro | Cyberknife | 8-12Gy x 3F | 43.2-60 | 14.3 | 9.6 by CT | NR | NR | 78% (24 mon) |
| Chang (24) | BRPC | 2 | Retro | Cyberknife | 25Gy x 1F | 87.5 | 6.3 | NR | 21% | 9% | 84 %(12 mon) |
| | LA | 56 | | | | | 6.7 | | | | |
| | Metastatic | 15 | | | | | 4.7 | | | | |
| Didolkar (10) | LA | 71 | Retro | Cyberknife | 10Gy x 3-5F | 22.5-60 | 13.4 LA 8.7 (whole group) | NR | 50% LA 30.5% | NR | 92% (8 mon) |
| | Local recurrence | 14 | | | | | | | | | |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Rwigema (25) | Adjuvant | 12 | Retro | Cyberknife | 18-24Gy x 1F | 50.4-81.6 | 20.6 | 9.7 | 81.8% | NR | 70.7% (12m) |
| | LNPC | 40 | | | | | 6.2 | 3.0 | 33% | | 38% (12 m) |
| | Recurrence | 11 | | | | | 13.3 | 3.1 | 58.4% | | 18.8 % (12 m) |
| | Metastatic | 8 | | | | | 3.4 | 2.8 | 0% | | 40% (12 m) |
| Koong (26) | LA | 15 | ph I | Cyberknife | 15-25Gy x 1F | 37.5-87.5 | 11 | 2 | NR | NR | 100 % (5 mon) |
| Koong (27) | LA | 19 | ph II | Cyberknife | 25Gy x 1F boost after CRT 1.8 Gy/28F | 140.6 | 8.3 | 4.5 | 15% | 8% | 94% (8 mon) |
| Schellenberg(28) | LA | 20 | ph II | Cyberknife | 25Gy x 1F | 87.5 | 11.8 | 9.2 | 50% | NR | 94% (12 mon) |
| Schellenberg (29) | LA | 16 | ph II | Cyberknife | 25Gy x 1F | 87.5 | 11.4 | 9 | 50% | NR | 100 % (12 mon) |
| Hoyer (9) | LA | 22 | ph II | SBF | 15Gy x 3F | 112.5 | 5.7 | 4.8 | 5% | 9% | 57% (6 mon) |
| Polistina (30) | LA | 23 | ph II | Cyberknife | 10Gy x 3F | 60 | 10.6 | 7.3 | 39.10 % | NR | 50% (12 mon) |
| Liauw (11) | LA | 15 | Ph I/II | Fiducials | 10, 12.5, 15 Gy x 3F | 60-112.5 | 12.8 | 7 | 53% | 33% | 80% (12 mon) |
| Huguet (31) (GERCOR) | LA | 72 | Retro | | | | 15 | 10.8 | 65.30 % | NR | NR |

(see abbreviations table above)

**Table2. Borderline resectable and locally advanced pancreatic cancer studies (toxicity)**

| Study | no | RT technique | BED (Gy) | Acute G3 toxicity | Late G3-4 toxicity | pCR | R0 |
|---|---|---|---|---|---|---|---|

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Chuong (20) | 30 | Fiducials | 37.5-48 | 0% | 0% | 6.7% | 95.2% |
| Chuong (21) | 73 | Fiducials | 37.5-48 | 0% | 18.8% | 9.3% (BRPC)<br>0% (LANCP) | 96.9% (BRPC)<br>0% (LANPC) |
| Mahadevan (22) | 39 | Cyberknife | 43.2-60 | 0% | 9% | - | - |
| Mahadevan (23) | 36 | Cyberknife | 43.2-60 | 8% | 6% | - | - |
| Chang (24) | 77 | Cyberknife | 87.5 | 1.3% | 7.8% | - | 1.2% |
| Didolkar (10) | 85 | Cyberknife | 22.5-60 | 22.30% | 22.30% | - | - |
| Rwigema (25) | 71 | Cyberknife | 50.4-81.6 | 4.20% | 0% | - | - |
| Koong (26) | 15 | Cyberknife | 37.5-87.5 | 0% | 0% | - | - |
| Koong (27) | 19 | Cyberknife | 140.6 | 10.50% | NR | - | - |
| Schellenberg (28) | 20 | Cyberknife | 87.5 | 0% | 5% | - | - |
| Schellenberg (29) | 16 | Cyberknife | 87.5 | 6.25% | 12.50% | - | - |
| Hoyer (9) | 22 | SBF | 112.5 | 78% | 33% | - | - |
| Polistina (30) | 23 | Cyberknife | 60 | 0% | 0% | 0% | 8.6% |
| Liauw (11) | 15 | Fiducials | 60-112.5 | 0% | 27% | - | - |
| Huguet (31) (GERCOR) | 72 | | | NR | NR | | |

## 2 TRIAL DESIGN

The aim of the trial is to assess safety of extreme hypofractionation of SBRT using MRgRT in pancreatic cancer. The 5-, 3- and single fraction MRgRT treatments will be assessed as independent cohorts to determine if each one is tolerable. Tolerability will be assessed using conjugate posterior beta distributions.

This is a 3-arm uncontrolled non-randomised safety study. There are three phases to recruitment for this study: an initial safety run-in, a focussed recruitment phase, and an expansion phase. A recruitment pause may be implemented in any phase for any regimen if deemed necessary by the TMG at any time. The assigned choice is dependent on the order the patient is referred.

In the initial safety run-in, 3 patients will be recruited into the 5-fraction regimen. The 3-fraction regimen will open immediately once three patients have been recruited into 5-fraction regimen. Once three patients have been accrued to the 3-fraction regimen, the single fraction regimen can open immediately. Recruitment to the 1- and 3-fractions regimens will pause while waiting for 3 months DLT follow-up from the first three patients in each cohort. It is possible both the 1 and 3 fraction regimens will be paused at the same time. Any patients recruited whilst both 1- and 3-fractions regimens are paused will be assigned the 5-fraction regimen.

Following the safety run-in, the focussed recruitment will start. Recruitment will continue in cohorts of 3 alternating between the 3- and 1-fraction regimens until a total of 12 patients in the 1- and 3-fraction regimens have been recruited. Recruitment to this phase will be continuous. After 3 patients' full DLT follow-up data in any regimen, the beta binomial model for that regimen can be run to assess the safety stopping rule in the event of a DLT or any other appropriate reason from the TMG.

For the remainder of the trial, recruitment will be in cohorts of 1 to all three regimens and recruitment will be continuous, alternating between 1-, 3-, and 5-fractions. Where plans that meet dose constraints are unable to be generated for single fraction regimens that patient will be assigned to the 3-fraction regimen or alternatively the 5-fraction regimen if recruitment to the 3-fraction cohort is paused or closed. Where plans that meet dose constraints are unable to be generated for 3-fraction regimens, that patient will be assigned to the 5-fraction regimen.
These patients will be included in the main analysis for the regimen they are treated in. A sensitivity analysis will be performed excluding these patients as they may be at higher risk of toxicity.

A regimen is declared safe if that regimen does not stop early due to toxicity, details on how this is decided are in the Statistical considerations section.

**Refer to the schedule of events for details of the study visits and procedures.**

### 2.1 Patient evaluability and replacement

No replacements are relevant or required for this study. Patients will be evaluable for the toxicity endpoints if one fraction is commenced.

### 2.2 Duration of patient participation

Patients will participate in screening and baseline assessments over the course of 1 month. MRgRT is then completed within 1- 3 weeks. Patients will then be followed for a minimum of 3 months from start of RT fand a maximum of 2 years from start of MRgRT for collection of outcome data. For most patients where the end of trial occurs before this timepoint their follow up will be shorter, but there will be a minimum of 3 months follow up.

### 2.3 Post-study care and follow-up

Following the final MR Linac treatment visit, patient follow-up and care will take place as standard practice. In addition, patients will be followed for a minimum of 3 months to complete research follow-up data collection on the 3 month DLT window. Additionally, as part of research follow-up, there will be collection of follow-up data by the site for the duration of the study up to 2 years follow up. Data will be recorded in the patient medical record for extraction onto the CRF. Available tumour control data (including local control) on follow up CT scans will also be collected. Participants will come off study at 2 years post registration or end of trial, whichever comes sooner.

Refer to the schedule of events and flow chart for details of the study visits and procedures.

## 3 OBJECTIVES AND ENDPOINTS

| Primary Objective | Endpoints/ Outcome measures | Time point(s) of evaluation of this end point |
|---|---|---|
| To establish the safety of MR-guided dose escalated and extreme hypofractionated SBRT in Locally Advanced pancreatic cancer | Dose Limiting Toxicity (DLT) | up to 3 months from start of MRgRT |
| **Secondary Objectives** | **Endpoints** | |
| Assess efficacy of MRgRT | • Overall survival (OS)<br>• Progression free survival (PFS)<br>• Local progression free survival | • Up to 24 months follow-up |
| For those undergoing surgery:<br>• Assess resection rates<br>• Assess resection margin status<br>• Assess response rates | • Resection rate<br>• R0/R1/R2 resection margin rates<br>• Rate of pathological complete response | • Surgery<br>• Pathological specimen evaluated at surgery<br>• Pathological specimen evaluation post op |
| Assess long term toxicity rates | • Any Late GI AE/other AE >grade2 CTCAE V5.0 | >3 months up to 24 months post start of MRgRT |
| Freedom from further chemotherapy* | Time from completion of RT to re-start of further chemotherapy | Anytime from start of MRgRT up to 24 months |
| **Tertiary/Exploratory Objectives** | **Endpoints** | |
| Identify a biomarker derived from imaging analysis and other associated clinical and pathological data which predicts outcome from RT | Features derived from images (for instance measures of perfusion or computer derived image features)<br>Blood assessments (where available) | In separate imaging manual |

* Patients where chemotherapy post MRgRT is offered pre-emptively as maintenance/ adjuvant (in absence of disease progression) will be excluded from this analysis

## 4 PATIENT SELECTION

Written informed consent must be obtained before any study specific procedures are performed. The Investigator will determine patient eligibility based on the following criteria.

### 4.1 Eligibility criteria for entry into the main study

#### 4.1.1 Inclusion criteria:

A patient will be eligible for inclusion in this study if all of the following criteria apply.

1. Participants must be fit and scheduled to receive MRgRT for pancreatic cancer. There are no specific restrictions on tumour size, number or interval from diagnosis.
2. Localised pancreatic cancer, which may be
    a. locally advanced and inoperable pancreatic cancer
    b. inoperable on medical grounds
    c. operable, but patient declines surgery
    d. locally recurrent pancreatic cancer

3. Histologically proven pancreatic ductal adenocarcinoma or cytological proven pancreatic malignancy. Where histology/cytology is ‘suspicious’ MDT should confirm that it is appropriate to treat as malignancy.

4. Male or Female, aged 16 years or above.
5. Life expectancy of at least 6 months.
6. ECOG performance status 0- 1.
7. Haematological and biochemical indices within defined ranges:

| Lab Test | Value required |
|---|---|
| Haemoglobin (Hb) | ≥ 8.0 g/dL |
| Platelet count | ≥50 x $10^9$/l; |
| Neutrophils | ≥ 1.0 x $10^9$/l. |
| Total bilirubin | ≤ 1.5 x IULN |
| AST(SGOT) or ALT(SGPT) | ≤ 3.0 x IULN |

8. Able (in the investigators' opinion) and willing to comply with all study requirements for the duration of the study.
9. Willing and able to give informed consent.

#### 4.1.2 Exclusion criteria:

A patient will not be eligible for the trial if any of the following apply:

1. Patients with specific MRI exclusion criteria – metallic implants, shrapnel, claustrophobia or other expected intolerance of prolonged (up to 90 minutes) stay in MRI scanner.
2. Prior radiotherapy to the upper abdomen
3. Pregnant or breast-feeding women, or women of childbearing potential unless effective methods of contraception are used. Male patients who do not agree to use a condom during RT treatment and for three months after or who are not surgically sterile.
4. Distant metastatic disease or local disease that cannot be encompassed in the SBRT field.

### 4.2 Protocol waivers to entry criteria

Protocol adherence is a fundamental part of the conduct of a clinical study. Changes to the approved protocol need prior approval unless for urgent safety reasons.

Before entering a patient onto the trial, the Principal Investigator or designee will confirm eligibility. If unsure whether the patient satisfies all the entry criteria and to clarify matters of clinical discretion, investigators must contact the Trial office, who will contact the Chief Investigator or designated clinicians as necessary. If in any doubt the Chief Investigator must be consulted before entering the patient. Details of the query and outcome of the decision must be documented in the TMF and Source

Investigators should not request a protocol waiver to enter a patient who does not satisfy the selection criteria.

### 4.3 Re-screening if patient does not meet inclusion/exclusion criteria first time round

Screening failures are ineligible and will not be rescreened.

### 4.4 Clinical queries and protocol clarifications

Every care has been taken in drafting this protocol. Contact the trial office for clarification if any instructions seem ambiguous, contradictory or impractical. Clinical queries must also be directed to the trial office. All clinical queries and clarification requests will be logged, assessed and a written response provided. Minor administrative corrections or clarifications will be communicated to all trial investigators for information as necessary. For urgent safety measures or changes that require protocol amendment see section 22.3 and 22.4 below.

### 4.5 Patient registration procedure

Potential participants will be identified from participating Trusts and their referring network of collaborators. These NHS referral pathways are in use currently for SABR treatments under existing CtE rules and will continue under the planned Cancer alliances.

Patients considered by their Clinical Oncologist to be potentially suitable for MR Linac based treatment (and therefore potentially eligible for the study) will be considered by designated MDTs. This may be an NHS MDT for SABR, and for upper GI cancer patients. Patients considered suitable for MR Linac based treatment by the MDT will then be contacted about the study. The recommended pathway is that potential patients are provided the PIS by email and a telephone appointment with them is made to review whether the patient is interested in the trial and also if suitable for MR Linac. Patients will then either be booked into a normal clinic, or if interested and suitable for MR Linac, an appointment will be made with the relevant clinical oncologist and the hospital trials unit to carry out informed consent and then the screening assessments on the same day (for those who do consent to the study), as per the schedule of Assessments.

Once the patient is confirmed eligible they will be registered on the study and MR Linac treatment planning will then commence. Patients not wishing to consent will still receive treatment on the MR Linac on a purely clinical basis with no research data collected.

A screening log must be kept of all patients considered for the study including any that are subsequently excluded; the reason for exclusion must be recorded on this form. A copy of the screening log should be sent to the trial office on request, but without patient identifiers. The original must be retained on site.

Before entering a patient onto the study the Principal Investigator or designee will confirm eligibility. If in any doubt the Chief Investigator must be consulted before entering the patient.

**Registration procedure:** Refer to EMERALD Site Registration Procedure located in the ISF for complete details.

## 5 TRIAL CONSENT AND CONTRACEPTION COUNSELLING

Please refer to the Schedule of Investigations given at the front of this protocol. Details of all protocol evaluations and investigations must be recorded in the patient's medical record for extraction onto the CRF.

### 5.1 Informed consent

Potential participants will be given the current, approved version of the patient information sheet. They will also receive clear verbal information about the study detailing no less than: the nature of the study; the implications and constraints of the protocol; the known side effects and any risks involved in taking part. It will be explained that they will be free to withdraw from the study at any time, for any reason, without prejudice to future care, and with no obligation to give a reason for withdrawal. They will have adequate time to consider the information provided and the opportunity to question the Investigator, their GP or other independent parties before deciding whether to participate.

The Investigator (or delegate) who obtains consent must be suitably qualified and experienced and can include radiographers if appropriately trained. All delegates working on behalf of the investigator must be authorised by the PI. The Investigator is responsible for ensuring that the trial consent procedures comply with the principles of GCP. Informed consent discussions and outcomes must be well documented in the medical record. The Investigator (or delegate) must be satisfied that the patient has made an informed decision before taking consent. The patient and the Investigator (or delegate) must personally sign and date the current approved version of the informed consent form in each other's presence. A copy of the information and signed consent form will be given to the participant. The original signed form will be retained at the trial site in the Investigator Site File, with a copy held in the medical record.

### 5.2 Contraception and pregnancy testing

All participants must be advised on the need to use reliable methods of contraception while receiving RT treatment. The advice should include:

- The definition of women of childbearing potential and of fertile men:
  A woman is considered of childbearing potential (WOCBP), i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilisation methods include

hysterectomy, bilateral salpingectomy and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

A man is considered fertile after puberty unless permanently sterile by bilateral orchidectomy.

- The requirement for pregnancy testing prior to commencing RT
- The acceptable methods, including:
    - Complete abstinence i.e. refraining from heterosexual intercourse whilst receiving RT as per standard of care for RT.
    - Vasectomy (male) or vasectomised partner (WOCBP) with documented azoospermia 90 days after procedure
    - Progesterone only hormonal contraception associated with inhibition of ovulation
    - Hormonal contraception including combined oral contraceptive pills, vaginal ring, injectables, implants and intrauterine devices (IUDs)
    - Intrauterine hormone-releasing system (IUS)
    - Non-hormonal IUD
    - Bilateral tubal occlusion
- Males who are azoospermic are exempt from contraceptive requirements.
- The recommendation that a barrier method should be used in addition to another form of contraception.
- Males being treated with Temozolomide (TMZ) who are sexually active with WOCBP should take these precautions whilst receiving RT and to seek advice on cryoconservation of sperm prior to treatment.
- Females should to take these precautions whilst receiving RT and for the following 6 months.

### 5.3 Pregnancy Counselling

Female participants of child-bearing potential should be appropriately counselled that there is a risk to an unborn child and that pregnancies will be followed up. This will include accessing the mother and child's notes for female participants. Male participants should be aware that treatment could damage sperm.

Any pregnancy (also applies to females partners of male trial participants) occurring during RT treatment will be followed up and the outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth or congenital abnormality) will be reported and followed up even if participant is discontinued from the trial early.

## 6 TRIAL PROCEDURES AND ASSESSMENTS

Please refer to the Summary Schedule of Events given at the front of this protocol. Details of all protocol evaluations and investigations must be recorded in the patient's medical record for extraction onto the CRF.

Results of research imaging are exempted from this requirement, these will be stored separately and not fed back to the patient's clinical care team. Arrangements will be put in place to ensure the appropriate storage and archiving of the research imaging results.

In the sub-sections below details are provided of all assessments to be carried out on study.

### 6.1 Screening and baseline assessments

All screening for eligibility and baseline assessments must be performed/obtained within the 28 days before the patient receives the MR planning scan.

- **Written informed consent** see section 5.1 for details.
- **Demographic details** to include age and sex
- **Referring Hospital and referring consultant for retrieval of post-trial SoC CT scans**
- **Medical History** as considered appropriate by clinician, making sure the patient meets appropriate eligibility criteria. Include date of diagnosis of pancreatic cancer.
- **Clinical review and disease assessment:** as considered appropriate by clinician
- **Haematology** - FBC
- **Biochemistry** – sodium, potassium, urea, creatinine, ALT or AST, Bilirubin, Albumin, alkaline phosphatase.

- **Ca19.9 tumour marker**
- **eGFR**
- **Urine pregnancy test** (for females of child bearing potential only)
- **ECOG Performance Status**
- **Baseline Sign and Symptoms**: provide date of onset, event diagnosis (if known) or sign/symptom, severity, time course. Terms should be specific medical terms according to NCI CTCAE version 5. Please avoid using abbreviations, combined terms e.g. nausea and vomiting and ambiguous terms e.g. deranged, abnormal.

### 6.2 Evaluations during the study

**Planning scan visit**

- **Collection of Clinical Mode MR Linac data**, including replanning data. Anonymised copies to be provided to the Trial Office.
- **AE Review**: provide date of onset, event diagnosis (if known) or sign/symptom, severity, time course, duration and outcome and relationship to study intervention. Terms should be specific medical terms according to NCI CTCAE version 5. Please avoid using abbreviations, combined terms e.g. nausea and vomiting and ambiguous terms e.g. deranged, abnormal.

**During MR Linac Treatment**

- **Collection of Clinical Mode MR Linac data**, including replanning data. Anonymised copies to be provided to the Trial Office.
- **ECOG status prior to fraction 1**
- **AE Review**: provide date of onset, event diagnosis (if known) or sign/symptom, severity, time course, duration and outcome and relationship to RT or other study intervention. Terms should be specific medical terms according to NCI CTCAE version 5. Please avoid using abbreviations, combined terms e.g. nausea and vomiting and ambiguous terms e.g. deranged, abnormal.
- **DLT Review** (see section 10.2)

### 6.3 During Follow up

The first follow up visit is at 1 weeks (+/- 4 days) post last fraction of radiotherapy. Subsequent visits are at 3 weeks (+/- 1 weeks), 6 weeks (+/- 2 weeks), 3 (+/- 1 month), 6 (+/- 1 month), 12 (+/- 1 month), and 18 (+/- 1 month) months post first fraction of RT treatment and at local relapse, with end of study visit performed up to 24 months post RT Fraction #1/Start of treatment.

The follow-up visits may be conducted either in person, or remotely via telephone call or internet video/audio call. Participants should be invited to attend the 3 week and 3 month follow up visits in person at site, if possible. However, this is not mandatory. If a patient elects to have their 3 month follow-up visit remotely, blood samples for standard of care assessments (including Ca19.9 tumour marker analysis) should be collected via a suitable alternative local to the patient, and results reported in the appropriate CRF.

**Follow-up visits include:**

- **Clinical review and disease assessment for progression**
- **AE review**: collection of all AEs until 3 months follow-up visit. From this point onwards, AEs related to MRgRT only should be captured in the CRF. AE review documentation should identify AEs considered related to MRgRT.
- **DLT Review** (See section 10.2) until 3 months follow-up visit.
- **Late-onset Severe Toxicities Review** (See section 10.30) Follow-up visits (where applicable) beyond 3 months follow-up visit.
- **Routine CT scan** (at 3, 6, 12 months post radiotherapy and progression), this may be done at the patient's local site and the images and report transferred to the study site.
- **Chemotherapy**: (At 3 months visit onwards) Date of start of any post MRgRT chemotherapy other than planned adjuvant or maintenance chemotherapy

- **Surgery***: (*At 3 months visit onwards) For those who undergo surgery, collection on resection rate, resection margin status (R0/R1/R2), response rate.
- **Haematology** (3-Month visit only) - FBC
- **Biochemistry** (3-Month visit only) – sodium, potassium, urea, creatinine, ALT or AST, Bilirubin, Albumin, alkaline phosphatase
- **Ca19.9 tumour marker** (3-Month visit only)

### 6.4 End of study evaluations at end of study, 24 months follow-up or death*

At end of study (+/- 1 Months) the following data will be collected (data from medical records no visit):

- **AE review**: collection of all AEs until 3 months follow-up visit. From this point onwards, AEs related to MRgRT only should be captured in the CRF. AE review documentation should identify AEs considered related to MRgRT.
- **Late-onset Severe Toxicities Review** (See section 10.30) Follow-up visits (where applicable) beyond 3 months follow-up visit.
- Local control in the treated site
- Overall disease control
- Survival status
- Chemotherapy: Date of start of any post MRgRT chemotherapy other than planned adjuvant or maintenance chemotherapy

*for participants on study less than 24 months prior to study closure this data will be collected at an earlier timepoint (at a minimum of 3 months follow-up and as close as possible to study closure).

### 6.5 Evaluations on early withdrawal

The following evaluations should be carried out on early withdrawal from the study:

- AE review
- DLT review (if early withdrawal is within 3-month DLT window)
- Late-onset severe toxicities review (if early withdrawal takes placed after 3-month DLT window)
- Local control in the treated site
- Overall disease control
- Reason for withdrawal

### 6.6 Data Transfer

After participant registration and at suitable timepoints during the study, unless deemed not relevant by the TMG, copies of imaging and related non-imaging data as follows should be transferred following the Imaging Transfer Manual to Oxford University to the Imaging Research Database or the Trial office Trial Master File as instructed, for further analysis:

- Baseline imaging data including standard of care diagnostic CT and optional MRI used as baseline imaging and whole-body PET-CT if performed in routine care
- Clinical Mode MR Linac data
- Planning 0.35T MRI scans
- On treatment images, plan adaptation
- CT scan (Imaging and clinical Report) at 3, 6 and 12 months &/or relapse

## 7 EARLY PATIENT WITHDRAWAL

### 7.1 Treatment Withdrawal

During the course of the trial, a patient may withdraw early from the study. This may happen for a number of reasons, including:

- AEs requiring discontinuation
- Clinical decision
- Patient decision (it is important this is distinguished from consent withdrawal in the patient notes)
- Loss to follow-up
- Significant protocol deviation or inability to comply with trial procedures

If the patient stops the MR guided RT early, the treatment eCRF needs to be completed, and all other relevant CRFs including the AE CRF. The reason for withdrawing from treatment early should be clearly documented in the medical records.

### 7.2 Consent Withdrawal

Consent withdrawal means that a patient has expressed a wish to withdraw from the study altogether including any future follow up. Under these circumstances, the site needs to document all relevant discussions in the patient notes. It is important to document clearly that the participant is aware that their data/samples collected prior to consent withdrawal will still be used as part of the study. No subsequent data (including routine care data) should be captured in the CRF. The site should notify the Trial Office, which will allow the office to mark all future CRFs as not applicable. Under these conditions, investigators are still responsible to follow up any SUSARs till resolution.

### 7.3 Consent withdrawal to follow-up assessments/visits only

Participants may withdraw consent to follow-up assessments or visits only, in these cases it should be clarified and documented in the patient notes whether follow-up data may continue to be collected by review of the patient notes to capture endpoints of local control, progression, RT toxicity and overall survival.

## 8 SAMPLES FOR LABORATORY ANALYSIS

### 8.1 Samples to be analysed in local diagnostic laboratories

Samples for haematology and biochemistry analysis will be labelled with standard patient identifiers and sent to the local hospital/site diagnostic laboratory. Results will be processed in the standard way and entered into the routine hospital reporting system. Samples will be stored, held, reported and subsequently destroyed in accordance with standard local laboratory practice.

## 9 MRI

The Viewray MRIdian MR Linac[15] combines a 6 MV flattening-filter-free (FFF) linear accelerator, providing a 600 cGy/min. photon beam with a source-to-axis distance of 90cm, with a 0.35 T Siemens MRI scanner. In clinical mode, True Fast Imaging with Steady State Precession (TRUFISP) T2/T1-weighted sequences are used to provide the cine MRI (real-time imaging) for beam gating[16], and volumetric imaging for OARs[17] with in-plane resolutions of 3.5mm x 3.5mm and 1.5mm x 1.5mm respectively. In research mode, additional pulse sequences may be used to obtain imaging data in other modalities.

## 10 RADIOTHERAPY

Patients will receive radiotherapy on MR Linac according the trial radiotherapy guidance documents. These will specify the radiotherapy prescription, target coverage criteria and the critical OAR dose constraints for each fractionation scheme. Radiotherapy guidance documents will be submitted to the study TMG and approved.

All trial radiation therapy treatments will be delivered with an integrated MRI-RT delivery system (MRIdian Linac). SBRT fractions will be delivered ideally on alternate days, treating at least twice per week. Daily treatment is permissible with at least 18 hours between fractions for 5-fraction regimen (Chuong et al, 2020, https://doi.org/10.1016/j.ijrobp.2020.07.901).

As per section 6.2 and 6.6, copies of Clinical Mode MR Linac data, including replanning data, will be anonymised with Patient ID and provided to the Trial Office to be held in the Trial Master File.

**Treatment planning**

Patients will undergo a dedicated CT simulation, or MR simulation with suitable CT deformable registration or creation of a synthetic CT. Simulation will be performed with the patient immobilized in the selected treatment position. Use of dummy MRI coils is allowed. CT simulation including IV contrast is allowed. Prospective breathing management for

acquisition is recommended and can include shallow breathing, inspiration or expiration breath-hold according to institutional preference and experience. Scan slice thickness must be no greater than 3 mm. A dose grid resolution of 2mm or less must be used.

Detailed information on **treatment volumes, organs at risk and dose volume constraints** as well as **treatment delivery and on-table plan adaptation** is found in the radiotherapy guidance document.

**Treatment Delivery and on-table Plan Adaptation**
Briefly, every patient will receive radiation therapy according to the initial treatment plan using the MRIdian Linac system for alignment (image-guidance), dose prediction, tracking, gating and on-table adaptive planning when clinically indicated.

For each delivery fraction, a volumetric MRI data set will be obtained using system integrated sequences; the preferred sequence is a balanced gradient echo most similar to Siemens' True FISP scan with T2*/T1 weighted image-characteristics. The external contour of the patient should be inside the field of view.

The image set used for the simulation and initial treatment planning will be called the 'simulation image dataset.' The MRI dataset obtained at each fraction will be called the 'fraction image dataset.'

System integrated image registration between the simulation image dataset and the fraction image dataset will be performed. Original plan contours are propagated onto the respective fraction image dataset. All critical structures within a 3 cm axial and 2 cm craniocaudal distance from the surface of the original PTV will be re-contoured on the fraction image dataset. Tumour volume to be re-contoured at clinician discretion.

An estimated delivered dose will be calculated using the software on the console (dose prediction). An adapted radiation therapy plan must be generated. The adapted radiation therapy plan should be used according to guidance on the radiotherapy guidance document.

During radiation dose delivery, continuous cine MR image acquisition in at least one principal plane (suggested sagittal, but at the discretion of the treating physician) is mandatory for soft tissue tracking and radiation beam gating. To this end, a tracking slice will be positioned to include a cross-sectional cut of the target or suitable surrogate for intra-fractional soft tissue tracking. The tracking/gating volume will be delineated based on either the GTV or the PTV.

Breathing motion management will be employed. This will include shallow breathing and breath hold. Breath hold may be patient directed or based on staff coaching. Breath hold assistance devices such as use of mirrors to visualize a wall mounted monitor, MR compatible goggles or image projection into the bore for target positional visualization are allowable and encouraged for use.

**Research imaging manual**
The imaging manual provides detailed information on the required imaging/ Digital Images and Communications in Medicine (DICOM) dataset for the purpose of the trial. These will include standard-of-care (SOC) diagnostic imaging, pre-treatment and on-treatment radiotherapy, research imaging and follow-up imaging data. Research imaging sequences include: T1-weighted, T2-weighted, and DWI MRI sequences and others defined by the research team and what is clinically available on the MR Linac.

**Image capture and data storage**
All SOC setup images, images used for plan dose prediction and adaptive re-planning, and post-treatment imaging are to be saved and stored in the MRIdian system. All image data is to be backed up, and the pseudonymised data will be transferred to the University Research Server for permanent storage and later image analysis.

**Plan, predicted dose, adaptive plan and research imaging storage**
All clinically approved plans, structures delineated for dose prediction, as well as all adapted radiation therapy plans will be saved and stored in the dedicated software of the MRIdian system. We have shown we can generate these from the pseudonymised DICOM files in externally-developed software such as CERR (the Computational Environment for Radiotherapy Research) or using custom analysis code developed locally. The original DICOM files are also available in the GenesisCare Treatment Planning System (TPS). All initial plans, structures delineated initially and on-table adapted plan data is to be backed up for permanent storage and potential later institutional or centralized

analysis. Structure, radiation dose and radiation plan data storage will be based on institutional protocols but need to allow for anonymized data export to the university's Research Imaging Server for research analysis.

## 10.1 Hypofractionation

For each of the three fractionations (5,3,1) we have defined a single dose level (See Table 3). The starting regimen will be 50 Gy in 5 fractions (BED10 =100 Gy).

| Fractionation | Dose to PTV (Gy) | | |
|---|---|---|---|
| | Dose/# | Total dose | BED 10 |
| 5# | 10 | 50 | 100 |
| 3# | 13 | 39 | 90 |
| 1# | 25 | 25 | 88 |

Table 3: Radiotherapy levels. BED 10 biological equivalent dose for acute reacting tissues (α/β=10).

## 10.2 Dose limiting toxicity (DLT)

In this study, DLT is defined in the following list of possible SBRT treatment related AEs (defined according to CTCAE v5.0) seen in the period from starting SBRT treatment to 3 months post treatment.

DLT Events (within 3 months)

- Grade 3 upper gastro-intestinal bleeding
- Gastro-intestinal fistula (any grade)
- Grade 4 nausea/vomiting uncontrolled despite optimum anti-emetics
- Grade 4 pancreatitis not stent related
- Vascular events (where these are not considered to be tumour related)

### 10.3 Late-onset severe toxicities

Late-onset severe toxicities may occur and will be monitored for during follow up (>3 months and up to 24 months where trial remains open and/or patient on trial)

- >=Grade 3 upper GI bleed
- gastro-intestinal fistula (any grade)
- >= Grade 3 vascular events (where these are not considered to be tumour related)

### 10.4 Chemotherapy Guidance

At least 3 months of chemotherapy prior to RT is recommended but not mandated. Chemotherapy should be avoided for at least 2 weeks before and for 4 weeks after RT.

### 10.5 Support medication on commencing radiotherapy

Concomitant medication may be given as medically indicated. Recommendations as part of standard of care:

- Omeprazole: 20-40mg OD for 3 months
- metoclopramide 10mg PRN TDS
- Ondansetron 4mg PRN BD

# 11 EVALUATION OF RESPONSE

## 11.1 Measurement of disease for solid tumours

Routine imaging using standard of care CT scans will be used to evaluate disease status, noting specifically disease status within the radiation field, and any new sites of metastases. Local control in the radiation field is an endpoint for the imaging biomarker analysis tertiary/exploratory objective. This is defined as progressive disease occurring within or overlapping with the PTV of the RT treatment. Any routine scan reporting local recurrence following radiotherapy will be collected for central review to confirm the overlap of any progressing disease with the target volume (PTV). Sites will be responsible for requesting, pseudonymising and transferring the CT scan showing potential in field recurrence to the central database.

For the secondary endpoint of progression free survival, where feasible we will collect data from routine standard of care scans during follow to 12 months and at progression (where applicable), and rely on local reports to identify local or distant progression.

# 12 ASSESSMENT OF SAFETY

Patients in this study are receiving clinical care (radiotherapy on an MR Linac) which they would otherwise receive if not participating in the trial but with a higher radiotherapy dose and/or over fewer treatment days. MRI scans completed on the MR Linac are standard clinical care but with the addition of some sequences for research purposes. Safety is a primary endpoint.

The Investigator will monitor each patient for clinical and laboratory evidence of adverse events on a routine basis throughout the study. Should an Investigator become aware of any study intervention related SAEs following this period, these must also be reported as stated below. Adverse event monitoring starts from the planning scan visit until participant completes the trial. All reportable AEs will be followed to a satisfactory conclusion. Any reportable AEs that are unresolved at the patient's last visit in the study are followed up by the Investigator for as long as medically indicated, but without further recording in the CRF.

All AEs reported to the trial office will be processed according to internal SOPs. The trial office may request additional information for any AE as judged necessary.

## 12.1 Adverse Event Definitions

An **Adverse Event** or experience (AE) is any untoward medical occurrence in a patient or research study subject temporally associated with study participation.

AEs may be spontaneously reported by the patient and/or in response to an open question from study personnel or revealed by observation, physical examination, or other diagnostic procedures. Any clinically relevant deterioration in laboratory assessments or other clinical finding is considered an AE.

A **Serious Adverse Event (SAE)** is any AE that:

| | |
|---|---|
| • **Results in death** | |
| • **Is life-threatening** | This refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe. |
| • **Requires in-patient hospitalisation or prolongs existing inpatient hospitalisation** | In general, hospitalisation signifies that the subject has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out-patient setting. Complications that occur during hospitalisation are AEs. If |

| | |
|---|---|
| | a complication prolongs hospitalisation or fulfils any other serious criteria, the event is serious. When in doubt as to whether hospitalisation occurred or was necessary, the AE should be considered serious. |
| • **Results in persistent or significant incapacity or disability** | This means a substantial disruption of a person's ability to conduct normal life functions. It does not include experiences of relatively minor medical significance or accidental trauma (e.g. sprained ankle), which do not constitute a substantial disruption. |
| • **Is a congenital anomaly or birth defect** | |
| • **Is any other medically important event** | Defined as an event that may jeopardise the patient or may require intervention to prevent one of the outcomes listed above. |

**For reactions associated to a trial procedure or intervention:**

**Adverse Reaction/Response (AR)**
All untoward and unintended responses related to a trial intervention/procedure

**A Suspected Unexpected Serious Adverse Response/Reaction (SUSAR)** This is a term used to describe a serious adverse response/reaction to a trial procedure/intervention, the nature or severity of which is not listed in the protocol or other applicable information as an expected event.

**Reportable event**
An event which must be reported to the REC.

### 12.2 Determining adverse event causality

The Investigator will assess and classify the relationship of an AE to the trial interventions (MRI, RT) as follows:

| Classification | Relationship | Definition |
|---|---|---|
| **Related** | **Definitely** | • Starts within a time related to the study intervention *and*<br>• No obvious alternative medical explanation. |
| | **Probably** | • Starts within a time related to the study intervention administration *and*<br>• Cannot be reasonably explained by known characteristics of the patient's clinical state. |
| | **Possibly** | • Starts within a time related to the study intervention *and*<br>• A causal relationship between the intervention and the adverse event is at least a reasonable possibility. |
| **Not related** | **Probably not** | • The time association or the patient's clinical state is such that the study intervention is not likely to have had an association with the observed effect. |
| | **Definitely not** | • The AE is definitely not associated with the study intervention. |

The Investigator must endeavour to obtain sufficient information to confirm the causality of the adverse event and give their opinion of the causal relationship between each AE and each study intervention. This may require instituting supplementary investigations of significant AEs based on their clinical judgement of the likely causative factors and/or include seeking a further specialist opinion.

## 12.3 Expected adverse events

### 12.3.1 Expected adverse events for MRI

Adverse reactions associated with MRI are vertigo-like sensations, claustrophobia and noise intolerance. Expected MRI adverse reactions are non-serious and resolve once the subject is removed from the scanner. Any serious adverse reactions to the MRI would be considered unexpected.

### 12.3.2 Expected adverse events for radiotherapy in this study

MRgRT for pancreatic cancer is expected to cause the events listed below. Any of these events that are life-threatening are considered to be unexpected, where not considered to be tumour related.

**Event**
Abnormal liver function tests
Bile duct stricture*
Diarrhoea
Discomfort or Pain in the irradiated field
Duodenitis
Fatigue
Gastritis
Gastro-intestinal bleeding
Gastro-intestinal fistula*
Gastro-intestinal perforation*
Gastro-intestinal ulceration*
Hair loss
Lethargy
Localised inflammation
Loss of appetite
Loss of renal function*
Nausea
Obstructive jaundice
Oedema
Pancreatitis
Skin inflammation
Skin irritation
Vascular events (where these are not considered to be tumour related) *
Vomiting

*late events can occur immediately or beyond 3 months and will be reported up to end of study if life-threatening and related.

## 12.4 Events that must be reported on the SAE Form

All events that are serious and related to the trial interventions must be reported to the trial's office. All Dose Limiting Toxicities (DLTs) must be reported on the SAE form within 24 hours of becoming aware.

## 12.5 Events of special interest to be reported as SAEs

Radiotherapy toxicities grade ≤ 2 are exempt from SAE reporting unless they meet the below criteria:

1. Gastric/duodenal ulceration
2. Fistula

3. Perforation or bleeding

## 13 Suspected Unexpected Serious Adverse Reactions (SUSARs)

All SUSARs will be reported by the Trial Office (OCTO) to the REC and other parties as applicable. For fatal and life-threatening SUSARS, this will be done no later than 7 calendar days after the Sponsor or delegate is first aware of the reaction. Any additional relevant information will be reported within 8 calendar days of receiving the initial report. All other SUSARs will be reported within 15 calendar days.

### 13.1 Exemptions from reporting on the SAE form

Events that are unrelated to the trial interventions do not need to be reported. Events reported as SAEs which on investigation are confirmed as disease progression should be updated to progressive disease and will not be reported further as SAEs.

### 13.2 Reporting of SAEs to the Trials Office

SAEs must be reported to the trial office's pharmacovigilance office (contact details below) from day 1 of the study (planning scan visit) until the 3-month follow-up visit. After this point and until the participant is off study only SAEs associated with study intervention MRgRT should be recorded in the AE CRF, except for defined late-onset events that should continue to be reported as SAE's until the end of the trial. Any SAE that occurs at any time after the designated period that the Chief Investigators and/or sub-investigator consider to be related to the MRgRT must be reported to the pharmacovigilance office.

All SAEs must be reported on the trial-specific SAE Form and emailed to:

octo-safety@oncology.ox.ac.uk

SAE forms must be completed and submitted within 24hrs of becoming aware of the event. If the SAE has not been reported within the specified timeframe, a reason for lateness must be provided when sending the SAE Report Form. For the initial report the following elements must be completed:

- Overall diagnosis (NCI-CTCAE Version 5.0)
- Reason for seriousness
- Causality (must be assessed by a clinically qualified person)
- Name and signature of the reporting person

**Reporting to the Trust**

Investigators should also adhere to their local Trust policy for incident and SAE reporting in research.

### 13.3 Follow-up of SAEs

If new or amended information on a reported SAE becomes available, the Investigator can update the original form and initial and date all new or amended information so that all changes are clearly identified. If many changes are required the investigator should consider submitting the updated information on a new SAE form superseding the previous form. Follow up will continue until all the necessary safety data for the event has been gathered. Any related SAE that is ongoing when a subject completes his/her participation in the trial must be followed until any of the following occurs:

- The event resolves or stabilizes;
- The event returns to baseline condition or value (if a baseline value is available);
- The event is attributed to other agent(s) or to factors unrelated to study conduct.

### 13.4 Reporting Adverse Events on the CRF

All AEs, including Serious AEs must be recorded on the case report forms (CRF). Collection of all AEs starts from the Planning Scan visit and continues until the 3 months follow-up visit. After this point and until the participant is off study,

only AEs related to MRgRT should be recorded in AE CRF, except for defined late-onset events that should continue to be reported as SAE's until the end of the trial. AE review documentation should identify AEs considered related to MRgRTRT.

The information provided on every AE will include:

- event diagnosis (if known) or sign/symptom - terms should be specific medical terms. Abbreviations, combined terms e.g. nausea and vomiting and ambiguous terms e.g. deranged, abnormal, should be avoided.
- date of onset and of resolution
- severity - adverse events and toxicities must be graded according to the NCI Common Terminology Criteria for adverse events (NCI-CTCAE) Version 5.0.
- relationship of the AE to study intervention, RT
- seriousness
- outcome

Each separate AE episode must be recorded. For example, if an AE resolves completely or resolves to baseline and then recurs or worsens again, this must be recorded as a separate AE. For AEs to be considered intermittent, the events must be of similar nature and severity. Concomitant medication data is not required.

### 13.5 Events exempt from being reported as AEs

The following events are exempt from reporting on the AE CRF and will be captured on a separate CRF.

***Progression of underlying disease***

Disease progression and resultant death will be captured on the CRF as this is an endpoint of the study. Adverse events that are clearly consistent with disease progression will not be reported as individual AEs on the AE CRF. Clinical symptoms of progression will only be reported as adverse events if the symptom cannot be determined as exclusively due to the progression of the underlying malignancy, or does not fit the expected pattern of progression for the disease under study.

Every effort should be made to document the objective progression of underlying malignancy. In some cases, the determination of clinical progression may be based on symptomatic deterioration. For example, progression may be evident from clinical symptoms, but is not supported by tumour measurements. Or, the disease progression is so evident that the investigator may elect not to perform further disease assessments.

***Death on study***

Death due to disease under study is to be recorded on the Death CRF form providing the death is not unexpected or if a causal relationship suspected. The investigator must clearly state whether the death was expected or unexpected and whether a causal relationship to the study intervention is suspected.

### 13.6 Adverse Event Coding

All adverse event terms will be coded by OCTO using MedDRA version 25.0.

### 13.7 Informing Investigators of new safety information

The Trial office or the Chief Investigator will ensure that all investigators are kept informed in a timely manner, as new safety profile information becomes available. Investigators are responsible for briefing their study team and onward transmission to R&D office as appropriate.

### 13.8 Reporting increases in toxicity rates to the REC as unexpected events

Hypofractionation is expected to increase the frequency and severity of expected radiotherapy toxicities. A line listing of radiotherapy toxicities will be reviewed by the TMG once 6 patients have completed treatment and then 6 monthly. The TMG will determine if any rate increases are greater than expected and these will be reported to the REC as an unexpected event on the study SAE form.

### 13.9 Events that must be recorded on the AE CRF

All events that meet AEs classification (including SAE's) must be recorded on the AE CRF. For further details regarding reporting of AEs in the CRF see section 13.4.

## 14 PREGNANCY

Pregnancies (in a participant) occurring during the planning and treatment stage of the study must be reported using the Pregnancy Notification Form.

### 14.1 Maternal exposure

Women who become pregnant should be withdrawn from the interventions at the earliest opportunity. All reported pregnancies should be followed up until the outcome and for one month post-delivery. Pregnancy outcome must be recorded in the medical record and in the follow-up section of the Pregnancy Notification Form. Any abnormal outcome (other than elective abortion) for the mother or child should also be reported as a SAE.

### 14.2 Paternal Exposure

The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) should, if possible, be followed up and documented.

Where a report of pregnancy is received, prior to obtaining information about the pregnancy, the Investigator must obtain the consent of the subject's partner. Therefore, the local study team should adopt the generic ICF template in line with local procedures and submit it to the relevant Ethics Committees prior to use.

## 15 DEFINING THE END OF TRIAL

End of Trial will be 6 months from last patient last visit (LPLV) to allow for completing data collection, cleaning and sample analysis.

The LPLV will be the date on which the final patient attends for their final follow up assessment after their MR Linac treatment. This will be at least 3 months RT Fraction #1 and may be up until 24 months after treatment commences depending on the speed of recruitment.

The sponsor and the Chief Investigator reserve the right to terminate the study earlier at any time. In terminating the study, they must ensure that adequate consideration is given to the protection of the participants' best interests.

## 16 STATISTICAL CONSIDERATIONS

### 16.1 Sample size and power

#### 16.1.1 Sample Size based on the primary endpoint

The primary endpoint of the study is to establish the safety of 5-, 3- and single fraction MR-guided hypofractionation SBRT in localised pancreatic cancer by assessing DLTs.

A maximum of 60 evaluable patients will be included. There is no formal power calculation as this is a phase 1 trial, but simulations will be carried out to ensure the sample size is adequate.

#### 16.1.2 Statistical design

This is a hypofractionation study using conjugate posterior beta distributions to evaluate the safety of 5, 3 and single fraction using established dose constraints.

The three fraction regimens will be considered as three separate cohorts and analysed independently. The acceptable toxicity level is defined as 15% for each regimen. If the posterior probability of the DLT rate being above 15% is too high, (e.g. $P(\text{risk of DLT} > 0.15 \mid \text{Regimen, Data}) > \delta$ with $\delta$ defined using simulations before the start of the trial), that regimen will stop for safety. There is no early stopping for success.

A prior distribution will be specified for each regimen's toxicity rate. These priors will be beta distributions. As binary (0=No DLT, 1=DLT) toxicity data is accrued in each regimen, these priors will be updated to conjugate posterior beta distributions. These represent the distribution for the probability of DLT rate within a specific regimen based on all available data. It is from these posterior distributions that inferences about safety will be made. The three regimens will be analysed by three independent beta-binomial models. The priors are calibrated to ensure the models provide sensible posterior probabilities based on prior clinical knowledge and incoming trial data.

Only patients for whom we have full information (e.g. experienced a DLT or completed DLT follow-up window) will be included in the modelling.

Due to the low acceptable toxicity rate (15%) there is a concern a small number of DLTs early in the trial could result in the trial stopping for safety when in reality the treatment is safe. To reduce the possibility of erroneously stopping early, the model for each regimen will not run until 3 patients from that regimen have full toxicity information. **If there are safety concerns prior to this, the TMG may convene and decide the appropriate action.**

All other design parameters, such as cohort size, additional hypofractionation rules, stopping rules and maximum number of patients, are specified in section 16.2

The TMG will only assess the model for that regimen if a DLT occurs or at the committee's discretion after the first 6 patients in that regimen. The TMG may meet at any time in the trial to discuss safety concerns of any regimens.

### 16.1.3 Analysis of secondary endpoints

- **Overall/ progression free survival:** Defined as the time (date) between registration for this study and death/ progression. Patients alive/ not progressed at end of treatment will be censored. This will be reported using Kaplan Meier methods across all cohorts and per cohort (data permitting). OS/ PFS at 1 year will be reported along with the median survival.
- **Local and overall control rates:** Local and overall progression rates will be tabulated and presented by regimen. Time to progression, defined as the time (date) between registration for this study and date of first documented progression **or** death (whichever occurs first). Patients without progression or alive at end of treatment will be censored. This will be reported using Kaplan Meier methods across all cohorts and per cohort (data permitting).
- **Resection rates:** Definitive rate, R0/R1/R2 resection margin rate and pathological complete response rate will be tabulated and presented by regimen.
- **Long term toxicity rates:** Long term toxicity will be described using the adverse and serious adverse events occurring after the DLT window (> 3 months after starting treatment). All toxicities will be tabulated by type, grade and relatedness to the treatment. Toxicities may be presented graphically if appropriate.
- **Freedom from further line chemotherapy:** The proportion of patients who require further chemotherapy up to 24 months post start of treatment will be reported by regimen. Time from completion of radiotherapy to start of further chemotherapy will be presented using Kaplan Meier methods across all cohorts and per cohort (data permitting). Patients who do not require further chemotherapy by the end of follow-up will be censored.

## 16.2 Study design

**Refer to section 2. Trial Design.**

**Specific parameters:**

- 3 fractionation regimens
- Starting dose level = 1 for each regimen, starting regimen is 5 fractions
- Acceptable toxicity level = 0.15
- Cohort size = 3
- Maximum number of patients in the study = 60
- Early stopping for excessive toxicity only (defined as not satisfying the safety criterion on that regimen)
- Priors to be determined

Simulations will be used to assess the performance of the models, and tweak parameters as necessary to ensure the models performs well. Full details of the simulated performance of the design will be available a separate document.

**Dose selection during the trial**

The trial will start at the 5 fraction regimen (50Gy in 5 fractions). Recruitment will be continuous without pause, but after three participants have received 50Gy the other regimens will be open (3 fractions first then 1 fraction). Further to that, dose selection will alternate cohorts of 3 to the 1 and 3 fraction regimens until 12 patients have been recruited to both the 1- and 3- fraction regimens. Following that, recruitment will be in cohorts of 1 to all three regimens. Where patients cannot meet OAR constraints for the 1 fraction plan, patient will be assigned to the 3-fraction regimen or alternatively the 5-fraction regimen if recruitment to the 3-fraction cohort is paused or closed. Where plans that meet dose constraints are unable to be generated for 3-fraction regimens, that patient will be assigned to the 5-fraction regimen.

### 16.3 Early stopping

Each regimen will stop for safety if there is sufficient evidence it is too toxic (if P(risk of DLT > 0.15|, current data) > δ, δ to be defined using simulations).

Otherwise the maximum number of patients will be recruited or the recruitment period finishes.

#### 16.3.1 Importance of rapid data return

Analysis will be performed in real-time based on relevant available data to best inform the treatment to allocate to the next patient. The patient status update CRF is a custom built CRF that will capture all of the required data and should be entered promptly upon request, e.g. the next working day.

Data entered will also be used for safety monitoring. For these reasons, it is important that data is collected and made available on OpenClinica swiftly and no more than 5 working days of the initial event and within 14 days of receipt of a data query unless otherwise specified.

## 17 STATISTICAL ANALYSIS PLAN

No separate statistical analysis plan will be produced for this study. A document presenting simulation results finalising design parameters and a document detailing presentation of results will be used in its place. Sites must report any unintended deviations to OCTO according to the procedure outlined in site training.

### 17.1 Inclusion in analysis

All patients enrolled in the study and who received at least one dose of radiotherapy will be accounted for and included in the analyses. The number of patients who were not evaluable, who died or withdrew before treatment began will be recorded. The distribution of follow-up time will be described and the number of patients lost to follow-up will be given.

The analysis will include a description of patients who did not meet all the eligibility criteria, an assessment of protocol deviations, radiotherapy treatment and other data that impact on the general conduct of the study. Baseline characteristics will be summarised descriptively by regimen. Numbers (with percentages) for binary and categorical variables and means (and standard deviations), or medians (with lower and upper quartiles) for continuous variables will be presented. Patients who died or withdrew before treatment started or do not complete the required safety observations will be described and evaluated separately. Treatment related toxicity will be tabulated by type and grade of toxicity. All patients will be evaluable for toxicity from the time of their first treatment. Adverse events will be summarised by the number of patients experiencing each type of event. The grades and causality will be reported.

Patients will be analysed in the regimen they receive. For patients where plans are unable to be generated for a regimen and they are assigned a different regimen, they will be included in the main analyses for the regimen they receive. However, a sensitivity analysis is planned excluding them from this analysis population as they may be at higher risk of toxicity.

### 17.2 Subgroup analysis

No formal subgroup analyses are planned, any subgroup analyses performed will be labelled as exploratory and hypothesis generating.

### 17.3 Interim Analyses

The beta binomial model for a given regimen will be fitted if deemed necessary by the TMG, for example following a DLT. As this is a Bayesian analysis, continual reanalysis of the data does not inflate type I error.

### 17.4 Accounting for missing, unused, or spurious data.

Missing data for the primary outcome will be minimal, therefore any missing data will be described and not otherwise accounted for in the analysis.

### 17.5 Procedures for reporting any deviation(s) from the original statistical plan

Any deviations from the original statistical plan will be described and justified in the final report.

### 17.6 Final analysis

Based upon projected accrual rates, this trial is expected to complete recruitment within 1 year of opening to recruitment, but this may be extended into the follow up time if needed. Final analysis will be after all patients have been followed up for at least 3 months. Sensitivity analyses examining different priors and the effect this has on posterior estimates of toxicity will be presented. These extra analyses may also be presented in any interim analyses.

## 18 TRIAL COMMITTEES

### 18.1 Trial Management Group (TMG)

The Chief Investigator will chair a TMG responsible for overseeing the successful conduct and publication of the trial. The TMG will include Chief Investigator, Co-Investigators, Clinical Trial Manager, Trial Statistician and others as required. The TMG will meet as necessary to discuss toxicity data and to decide on opening the different regimens. TMG membership and decision-making procedures will be documented in the TMG charter.

### 18.2 Trial Steering Committee (TSC)

The Radiation and Imaging Oversight Committee (RIOC) will act as the TSC. The committee is chaired by an independent clinician and comprises other independent clinicians, a statistician and PPI representative. The role of RIOC is to provide oversight for the trial on behalf of the Sponsor and Funder. The TSC will provide overall supervision of the safe and effective conduct of the study. The TSC will review trial progress against agreed milestones, adherence to protocol, and patient safety, and consider new information. The TSC has the authority to recommend study closure where appropriate.

## 19 DATA MANAGEMENT

The data management aspects of the study are summarised here with details fully described in the Data Management Plan. See section on patient confidentiality for information on management of personal data.

### 19.1 Source data

Source documents are where data are first recorded, and from which participants' CRF data are obtained. These include, but are not limited to, hospital records (from which medical history and previous and concurrent medication may be summarised into the CRF), clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, electronic imaging data in DICOM or other format, and correspondence.

### 19.2 Case reports forms (CRFs)

The Investigator and study site staff will ensure that data collected on each participant is recorded in the CRF as accurately and completely as possible. The CRFs will not contain any source data. All appropriate laboratory data, summary reports and Investigator observations will be transcribed into the CRFs from the relevant medical record(s).

The investigator will ensure that:

- The relevant CRFs are completed.
- All CRF data are verifiable in the source documentation or the discrepancies must be explained.
- CRF sections are completed in a timely fashion, as close to the visit or event being recorded as possible.

- Data queries are resolved and documented by authorised study staff, giving a reason for the change or correction where appropriate.

The above considerations also apply to patients who are withdrawn early. If a patient withdraws from the study, the reason must be noted on the appropriate form and the patient must be followed-up as per protocol.

### 19.3 Accounting for missing, unused, or spurious data.

Missing data found will be chased up and supplemented where possible after consultation with the investigator. The control of the correctness of the data is performed with validity tests and consistency checks.

### 19.4 Non-CRF data

Imaging data and translational data may not be held in the CRF. The location of non-CRF data will be given in the trial specific Data Management Plan. Any source data that is not required to be transcribed into the CRF will be listed in the Data Management Plan.

### 19.5 Electronic Data Capture

Electronic data capture (EDC) and data management will be performed via a web-based, bespoke trial database (OpenClinica). OpenClinica is a dedicated and validated clinical trials database designed for electronic data capture. See: http://www.openclinica.org. The trial office will provide sites with instructions and a link to online training.

### 19.6 Source data table

| Primary Objective | Endpoint | Data required | CRF data[1] | Non-CRF[2] | Source data | Source data location |
|---|---|---|---|---|---|---|
| Safety of MR-guided hypofractionation SBRT in localised pancreatic cancer | Dose Limiting Toxicity (DLT) | Adverse events data | Yes | N/A | Patient notes | Patient notes |
| **Secondary Objectives** | **Endpoints** | **Data required** | **CRF data[1]** | **Non-CRF[2, 8]** | **Source data** | **Source data location** |
| Assess efficacy of MRgRT | Overall survival measured as days from start of MRgRT to death or survival at 2 years | Survival status at end of study | Yes | N/A | Patient notes | Patient notes |
| | Progression free survival: days from registration to first evidence of tumour progression (local or metastatic) using standard clinical reporting (RECIST criteria not required). | Outcome (SD, PD, PR etc.) | Yes[6] | Copy of pseudonymised CT scan transferred to OU research server for analysis. Data analysed and results saved in same server[7]<br>Copy of pseudonymised associated CT scan clinical report transferred to OCTO TMF. | CT scan | NHS site PACs |
| | Local control rate | Local progression of the treated lesion | No | Copy of pseudonymised CT scan transferred to OU research server for analysis. Data analysed and results saved in same server[7]<br>Copy of pseudonymised associated CT scan clinical report transferred to OCTO TMF. | CT scan | NHS site PACs |
| | Definitive resection rate; For those undergoing | Histology report | Yes | n/a | Histology report | NHS EPR |

| | | | | | | |
|---|---|---|---|---|---|---|
| | surgery: R0/R1/R2 resection margin rates; For those undergoing surgery: Rate of pathological complete response | | | | | |
| Assess long term toxicity | Toxicity Rates:<br>*All Grade 3+ toxicities to 12 weeks from end of RT<br>*Any late GI AE > grade 2 (CTC v5) after 12 weeks | Adverse Events | Yes | N/A | Patient notes | Patient notes |
| Freedom from further line chemotherapy | Time from completion of RT to re-start of further chemotherapy | Start date of chemotherapy regimen | Yes | N/A | Patient notes | Patient notes |
| **Exploratory Objectives** | **Endpoints** | **Data required** | **CRF data[1]** | **Non-CRF[2, 8]** | **Source data** | **Source data location** |
| Identify a biomarker derived from imaging analysis and other associated clinical and pathological data which predicts outcome from RT | imaging assessments | Imaging data | No | Baseline imaging, on treatment images, Clinical Mode MR Linac, including data replanning data | Pre treatment imaging<br>On treatment imaging | NHS PACS<br>MRiDian |

1 CRF data: captured in OpenClinica eCRF. Database held on server hosted by OpenClinica.com.
2 Non-CRF data: pseudoanonymised copy transferred from MR Linac machine or CT scanner to OU research server, except for CT Scan clinical report which are transferred pseudoanonymised to OCTO to be stored in TMF. Note: For the data that is not being collected in the OpenClinica CRFs, it is necessary to have quality control at every step: database validated, restricted access, version control, audit trail, evidence of training and qualification or supervision by trained & qualified person. Etc.
3 The NHS patient folder held at the GC site during treatment constitutes part of the NHS site Investigator Site File. It needs to be appropriately located within a restricted access room and should be returned to the main Investigator Site File held at the Trust once the participant completes their treatment at GC.
5 No equivalent copy returned to patient record: only a PDF printout of treatment providing actual dose delivered and area to which it was delivered, which are required for subsequent clinical care.
6 Site will perform standard of care reporting.
7 Results not returned to site as will not be required for subsequent clinical care.
8 Baseline imaging data including standard of care diagnostic CT and optional MRI used as baseline imaging and whole-body PET-CT if performed in routine care

## 20 CLINICAL STUDY REPORT

All clinical data will be presented at the end of the study as data listings. These will be checked to confirm the lists accurately represents the data collected during the course of the study. The trial data will then be locked and a final data listing produced. The clinical study report will be based on the final data listings. The locked trial data may then be used for analysis and publication. Analysis and publication of individual completed cohorts may take place prior to this.

## 21 STUDY SITE MANAGEMENT

### 21.1 Study site responsibilities

The Principal Investigator (the PI or lead clinician for the study site) has overall responsibility for conduct of the study, but may delegate responsibility where appropriate to suitably experienced and trained members of the study site team. All members of the study site team must complete the delegation log provided prior to undertaking any study duties. The PI must counter sign and date each entry in a timely manner, authorising staff to take on the delegated responsibilities. This must occur prior to the individual performing any research tasks. Staff training and sign-off for the MR Linac should follow GenesisCare and NHS Trust procedures.

### 21.2 Study site set up and activation

A Principal Investigator shall lead the study at their site, providing the local study office with all core documentation and attending a Site Training Call/Visit organized by the trial office before the site becomes activated (usually carried out as a telephone conference call or personal visit). The Trial Office will check that the site has all the required study information/documentation and is ready to recruit. The site will then be notified once they are activated on the trial management database and are able to begin recruiting patients.

### 21.3 Arrangements for sites outside the UK

It is not anticipated that this study will open in non-UK sites.

### 21.4 Study documentation

The trial office will provide an Investigator Site File to each investigational site containing the documents needed to initiate and conduct the study. The trial office must review and approve any local changes made to any study documentation including patient information and consent forms prior to use. Additional documentation generated during the course of the trial, including relevant communications must be retained in the site files as necessary to reconstruct the conduct of the trial.

### 21.5 Protocol deviations

Protocol compliance is fundamental to GCP. Changes to the approved protocol need prior approval unless for urgent safety reasons. The investigator must document and explain any deviations/violations from the current approved protocol. The investigator must promptly report any important deviation from Good Clinical Practice or protocol to the trial office by email. Examples of important deviations are those that might impact on patient safety, primary/ secondary endpoint data integrity, or be a possible serious breach of GCP (see serious breach section below).

## 22 ETHICAL CONSIDERATIONS

The sponsor and Investigators will ensure that this protocol will be conducted in compliance with the Principles of Good Clinical Practice (GCP) and the applicable policies of the sponsoring Institution and host trusts.

### 22.1 Ethical conduct of the trial and ethics approval

The protocol, patient information sheet, consent form and any other information that will be presented to potential trial patients (e.g. advertisements or information that supports or supplements the informed consent) will be reviewed and approved by an appropriately constituted, independent Research Ethics Committee (REC), HRA and host institution.

### 22.2 Research Governance

Once HRA & HCRW approval is in place for the trial, NHS sites will confirm capability and capacity to participate in the trial. This approval must be sent to the trials office.

### 22.3 Protocol amendments

Amendments are changes made to the research following initial approval. A 'substantial amendment' is an amendment to the terms of the REC application, or to the protocol or any other supporting documentation, that is likely to affect to a significant degree:

(1) the safety or physical or mental integrity of the subjects of the trial;
(2) the scientific value of the trial;
(3) the conduct or management of the trial; or
(4) the quality or safety of the NIMP/intervention used in the trial.

Non-substantial amendments are those where the change(s) involve only minor logistical or administrative aspects of the study.

All amendments will be generated and managed according to the trial office SOPs to ensure compliance with applicable requirements. Written confirmation of the REC and local approvals (where R&D choses to notify) must be in place prior to implementation by Investigators. The only exceptions are for changes that have been classified as non-notifiable to the trust and ones that are necessary to eliminate an immediate hazard to study patients (see below).

It is the Investigator's responsibility to update patients (or their authorised representatives, if applicable) whenever new information (in nature or severity) becomes available that might affect the patient's willingness to continue in the trial. The Investigator must ensure this is documented in the patient's medical notes and the patient is re-consented if appropriate.

### 22.4 Urgent safety measures

The sponsor or Investigator may take appropriate urgent safety measures to protect trial participants from any immediate hazard to their health or safety. Urgent safety measures may be taken without prior authorisation. The trial may continue with the urgent safety measures in place. **The Investigator must inform the trial office IMMEDIATELY if the study site initiates an urgent safety measure.**

The notification must include:

- Date of the urgent safety measure;
- Who took the decision; and
- Why the action was taken.

The Investigator will provide any other information that may be required to enable the trial office to report and manage the urgent safety measure in accordance with the current ethical requirements for expedited reporting.
The Trials office will follow written procedures to implement the changes accordingly.

### 22.5 Temporary halt

The sponsor and Investigators reserve the right to place recruitment to this protocol on hold for short periods for administrative reasons **or** to declare a temporary halt. A temporary halt is defined as a formal decision to:

- interrupt the treatment of subjects already in the trial for safety reasons;
- stop recruitment on safety grounds; or
- stop recruitment for any other reason(s) considered to meet the substantial amendment criteria, including possible impact on the feasibility of completing the trial in a timely manner.

The trial office will report the temporary halt via an expedited substantial amendment procedure to the REC. The trial may not restart after a temporary halt until a further substantial amendment to re-open is in place. If it is decided not to restart the trial this will be reported as an early termination.

### 22.6 Serious Breaches

Investigators must notify the trials office at once if any serious breach of GCP is suspected. A serious breach is defined as "A breach of GCP or the trial protocol which is likely to effect to a significant degree:

- the safety or physical or mental integrity of the subjects of the trial; or
- the scientific value of the trial"

In the event that a serious breach is suspected the Sponsor must be contacted within 1 working day. In collaboration with the C.I., the serious breach will be reviewed by the Sponsor and, if appropriate, the Sponsor will report it to the approving REC committee and the relevant NHS host organisation within seven calendar days.

### 22.7 REPORTS: Progress and End of Study Reports

This protocol will comply with all current applicable Research Ethics Committee and Sponsor requirements for the provision of periodic study safety and progress reports. Any additional reports will be provided on request. Reporting will be managed by the trials office according to internal SOPs. Sites will be urged to return as much data as possible before each database lock point.

The trial office will determine which reports need to be circulated to Principal Investigators and other interested parties according to internal SOPs. Study sites are responsible for forwarding trial reports they receive to their local Trust as required.

### 22.8 Transparency in Research

Prior to the recruitment of the first participant, the trial will have been registered on a publicly accessible database. Where the trial has been registered on multiple public platforms, the trial information will be kept up to date during the trial, and results will be uploaded to all those public registries within 12 months of the end of the trial declaration.

## 23 EXPENSES AND BENEFITS

There is no study funding to reimburse patient expenses incurred for attending additional research visits in excess of standard of care. Participating study sites may provide reasonable travel expenses as per local practice. The local arrangements will be explained to the patient during the informed consent discussions prior to trial entry.

## 24 QUALITY ASSURANCE

### 24.1 Risk assessment

This protocol is designed to deliver a risk-adapted approach to conducting the research. A risk assessment has been conducted and a monitoring plan will be prepared before the trial opens. The known and potential risks and benefits to participants have been assessed in comparison to those of standard of care. A risk management strategy is in place and will be reviewed and updated as necessary throughout the trial or in response to outcomes from monitoring activities. Monitoring plans will be amended as appropriate. Quality assurance of the treatment delivered will be included as part of the study.
Routine on-site monitoring is not planned however triggered visits may occur as required in response to triggers from central monitoring of the study. If triggered visits occur, data will be evaluated for compliance with the protocol and accuracy in relation to source documents.

Study sites will be monitored centrally by checking incoming data for compliance with the protocol, consistency, completeness and timing. The case report data will be validated using appropriate set criteria, range and verification checks. The study site must resolve all data queries in a timely manner. All queries relating to key outcome and safety data and any requiring further clarification will be referred back to the study site for resolution. For other non-critical data items, trial office staff may resolve data queries centrally providing the correct answer is clear. Such changes will be clearly identified in the CRF and the study site informed.

In the event of site visits reports will be sent to the site in a timely fashion and sites are expected to action any points highlighted in the report.

Radiotherapy trial Quality Assurance (RTQA)

RTQA will be conducted to ensure consistency of contouring and planning. All contours and plans will go through a peer-review process which includes a specialist upper GI radiologist and at least 2 upper GI clinical oncologists as per standard-of-care for current MR Linac plans. All on-trial clinical contouring including adaptive fraction contouring would be controlled by the CI/PI as to who was suitable to contour trial cases.

### 24.2 Audits

All aspects of the study conduct may be subject to internal or external quality assurance audit to ensure compliance with the protocol, GCP requirements and other applicable regulation or standards. Such audits may occur at any time during or after the completion of the study. Investigators and their host Institution(s) should understand that it is necessary to allow auditors direct access to all relevant documents, study facilities and to allocate their time and the time of their staff to facilitate the audit or inspection visit.

## 25 RECORDS RETENTION & ARCHIVING

During the clinical trial and after trial closure the Investigator must maintain adequate and accurate records to enable the conduct of a clinical trial and the quality of the research data to be evaluated and verified. All essential documents must be stored in such a way that ensures that they are readily available, upon request for the minimum period required by national legislation or for longer if needed. The medical files of trial subjects shall be retained in accordance with national legislation and in accordance with the host institution policy.

It is the University of Oxford's policy to store data for a minimum of 3 years after publication or public release of the research. Investigators may not archive or destroy study essential documents or samples without written instruction from the trial office. Trial data and associated metadata will be retained electronically in a suitable format in a secure server area maintained and backed up to the required standard. Access will be restricted to the responsible Archivist and will be controlled by a formal access request. On completion of the mandatory archiving period the TMF and associated archived data sets will be destroyed or transferred as appropriate, according to any data sharing requirements.

## 26 PATIENT CONFIDENTIALITY

The study will comply with the UK General Data Protection Regulation (UK GDPR) and Data Protection Act 2018, which require data to be de-identified as soon as it is practical to do so. Personal data recorded on all documents will be regarded as confidential. The processing of the personal data of participants will be minimised by making use of a unique participant study number only on all study documents and any electronic database(s), with the exception of the CRF, where participant year of birth will be added and the registration system where year of birth and initials will be included to appropriately identify individuals. The name and any other identifying detail will NOT be included in any trial data electronic file. All documents will be stored securely and only accessible by study staff and authorised personnel. The study staff will safeguard the privacy of participants' personal data. See section 18 Data Management for more details.

The Investigator site must maintain the patient's anonymity in all communications and reports related to the research. The Investigator site team must keep a separate log of enrolled patients' personal identification details as necessary to enable them to be tracked. These documents must be retained securely, in strict confidence. They form part of the Investigator Site File and are not to be released externally. All documents will be stored securely and only accessible by study staff and authorised personnel. The study staff will safeguard the privacy of participants' personal data.

Personal data breaches will be reported promptly to the University of Oxford's Central Data Breach Team (Data.breach@admin.ox.ac.uk ) as per our data protection obligations and notified to the site staff.

## 27 STUDY FUNDING

The study will be funded through the partnership between the University of Oxford and Genesis Care.

| Funder(s) | Financial and non-financial support given |
|---|---|
| MRC Institute for Radiation Oncology, Department of Oncology, University of Oxford | Support for personnel, and research costs |
| John Black Charitable Foundation | £3 million to enable access to treatment on MR Linac for NHS patients and research |
| University of Oxford/GenesisCare Collaboration fund, | Clinical trial research costs. |
| NHS England | Standard treatment costs for RT for NHS participants |

## 28 SPONSORSHIP AND INDEMNITY

### 28.1 Sponsorship

The Sponsor will provide written confirmation of Sponsorship. A separate study delegation agreement, setting out the responsibilities of the Chief Investigator and Sponsor will be put in place between the parties. The Oxford Clinical Trials Research Unit (OCTRU) will authorise the trial commencement once satisfied that all arrangements and approvals for the proper conduct of the trial are in place.

### 28.2 Indemnity

The University has a specialist insurance policy in place which would operate in the event of any participant suffering harm as a result of their involvement in the research (Newline Underwriting Management Ltd, at Lloyd's of London). NHS indemnity operates in respect of the clinical treatment that is provided.

### 28.3 Contracts/Agreements

This trial is subject to the Sponsor's policy requiring that written contracts/agreements are agreed formally by the participating bodies as appropriate. A Clinical Trial Agreement (CTA) will be placed between the Sponsor and participating organisations prior to site activation.

The Sponsor will also set up written agreements with any other external third parties involved in the conduct of the trial as appropriate.

### 28.4 Development of a new product/ process or the generation of intellectual property

Ownership of IP generated by employees of the University vests in the University. The University will ensure appropriate arrangements are in place as regards any new IP arising from the trial.

## 29 PUBLICATION POLICY

The sponsor will retain ownership of all data arising from the trial. The intention is to publish this research in a specialist peer reviewed scientific journal on completion of the study. The results may also be presented at scientific meetings and/or used for a thesis. The Investigators will be involved in reviewing drafts of the manuscripts, abstracts, press releases and any other publications arising from the trial and retain final editorial control. Authors will acknowledge that the study was Sponsored by and performed with the support of the Sponsor and other funding bodies as appropriate.

## APPENDIX 1: TABLE OF AMENDMENTS

| Amendment number | Amendment Description | Substantial amendment Y/N |
|---|---|---|
| 001 | • Optional Research Blood Sample removed<br>• Requirement for 3 Weeks and 3 months follow up visits to be face to face changed from mandatory to either face to face, or via telemed/telephone call.<br>• 3 Week Standard of Care Bloods (Haematology, Biochemistry, CA19.9 tumour marker) removed.<br>Minor Administrative changes:<br>• Lucinda Griffiths name removed as Trial Manager and replaced with Lynda Swan<br>• Medical Statistician's name changed and Lead Statistician's name added.<br>• Spelling of Histopathology' changed to 'Histology'.<br>• Dr Suliana Teoh's name removed as Lead Investigator.<br>• GenesisCare added as an affiliate to Professor Mukherjee's title.<br>• 'End of radiotherapy' changed to 'Completion of radiotherapy'.<br>• Omeprazole: 40mg OD changed to 20-40mg OD. | Y |

| | | |
|---|---|---|
| | • >= Grade 3 vascular events changed to >= Grade 3 vascular events (where these are not considered to be tumour related). | |

## APPENDIX 2: ECOG PERFORMANCE SCALE

| Activity Performance Description | Score |
|---|---|
| | |
| Fully active, able to carry out all on all pre-disease performance without restriction. | 0 |
| | |
| Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g. light housework, office work. | 1 |
| | |
| Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours. | 2 |
| | |
| Capable of only limited self-care. Confined to bed or chair more than 50% of waking hours. | 3 |
| | |
| Completely disabled. Cannot carry out any self-care. Totally confined to bed or chair. | 4 |

## APPENDIX 3: RESEARCH IMAGING

All images from EMERALD will be stored on the University research imaging server (IRIS). Analysis will be performed according to a separate overarching MR Linac imaging protocol. The following provides background to the imaging research approach.

Information about the different tissues present in a given region of an MR image can be extracted from an analysis of the relaxation properties of the hydrogen nuclei therein and their surrounding environment. Once the MR excitation pulse has been applied, the relaxation times of the longitudinal and transverse components of the hydrogen nucleis' net magnetisation is described by the T1 and T2 times respectively. Factors like water content (i.e. proton density) or the presence of other substances (e.g. oxygenated or deoxygenated blood) result in different intrinsic T1 and T2 times for different tissues, which is the underlying principle of T1-weighted and T2-weighted images. By altering the repetition time (TR) of the excitation pulse, and the echo time (TE) at which the MR signal is measured, the signals from different tissues can be emphasised or suppressed relative to each other depending on the imaging requirements. Because of their superior soft tissue contrast, high-resolution T2-weighted images are the gold standard for tumour staging in rectal cancers (32). However, the information present in these images can also be further analysed with two approaches: radiomics and Quantitative MRI (QMRI).

Quantitative MRI (QMRI) aims to extract biologically meaningful values from MR imaging. T2* mapping forms the basis of Blood Oxygen Level-Dependent (BOLD) MRI used in functional brain imaging. T2* differs from the "pure" T2 relaxation time by a constant that is influenced by the magnetisation properties of surrounding molecules – for example, oxygenated or deoxygenated blood. There is no squamous cell cancer data for T2* MRI, however in breast cancer, renal cancer, and prostate cancer some studies suggest T2* MRI could have a predictive value when performed during systemic therapy(33). Kremser et al. used snapshot FLASH T1 mapping in conjunction with an injected Contract Agent (CA) to study microcirculatory changes in tumours to predict the outcome of CRT in Primary Rectal Carcinoma (PRC) (34). More recently, sophisticated sequences that offer high-resolution T1-mapping on a timescale compatible with breath holds/peristaltic motion have been developed such as ShMOLLI (Shortened Modified Look-Locker Inversion Recovery)(35) and used in conjunction with T2* maps to predict clinical outcomes in patients with chronic liver disease (36, 37). The maps were used to estimate the extent of fibrosis in the liver. Fibrosis can also be a side-effect of CRT that can hinder the identification of response to treatment, as fibrotic and tumorous tissue appear similar on T2-weighted diagnostic scans (32). T1 and T2* maps of the tumour and surrounding regions, derived from sequences modified accordingly for the 0.35 T scanner of the Viewray MR Linac system, may therefore provide additional diagnostic information that may be used in its own right or as input for a (delta) radiomics-based analysis.

Diffusion Weighted MRI (DW MRI) provides information on the movement of water molecules in a given region of an MR image. In the context of oncology, restricted diffusion is due to hypercellularity seen in tumours. The b value represents this restriction in diffusion, in tumour tissue, in proportion to water movement in normal tissues; and depends on the strength and duration of applied magnetic field gradients. The Apparent Diffusion Coefficient (ADC) takes a number of b values to create a numeric value. A low ADC means restricted diffusion and is interpreted as reporting high cellularity (i.e. the presence of cancer). Historically, DW MRI has been investigated in squamous cell head and neck cancer. It is reported to allow differentiation between malignant and benign nodes(38, 39)(40), and it can differentiate between residual / recurrent disease and radiation fibrosis (41). There is also evidence that scanning at outset and during CRT is predictive of outcome (42, 43). With respect to rectal cancer, the ADC has been shown to improve diagnostic accuracy of response to CRT(43-46). Of most interest, however, are the recent small-scale studies using longitudinal DW imaging obtained during MRgRT treatment using the Viewray tri-Cobolt-60 system (47) and the Viewray MR Linac (48). These have shown promising results even with DW sequences adapted for the relatively low magnetic field strength of these systems. Obtaining similar data at the scale of the study described here would validate these results at the level required for clinical acceptance, and agree with similar studies of cervical cancer where the changes in ADC values over time correlated with the clinical and radiological response to CRT treatment (49).

**Radiomics** is the application of imaging processing and analysis techniques to visualisations of a given tumour or disease in order to extract meaningful features that may be correlated with clinical outcomes or other pathological characteristics. It is the natural progression of the clinician-driven, qualitative analysis of conventional MR imaging: there will be features present in the patterns of voxel intensities that are beyond the capabilities of the human eye to process and interpret. This study will provide a sufficiently large discovery set to enable machine learning techniques to be applied to the images to identify novel imaging biomarkers predictive of outcome at 12 months. A seminal paper by Lambin et al. outlined the possibilities of such an approach (50); they later went on to combine data from genomics

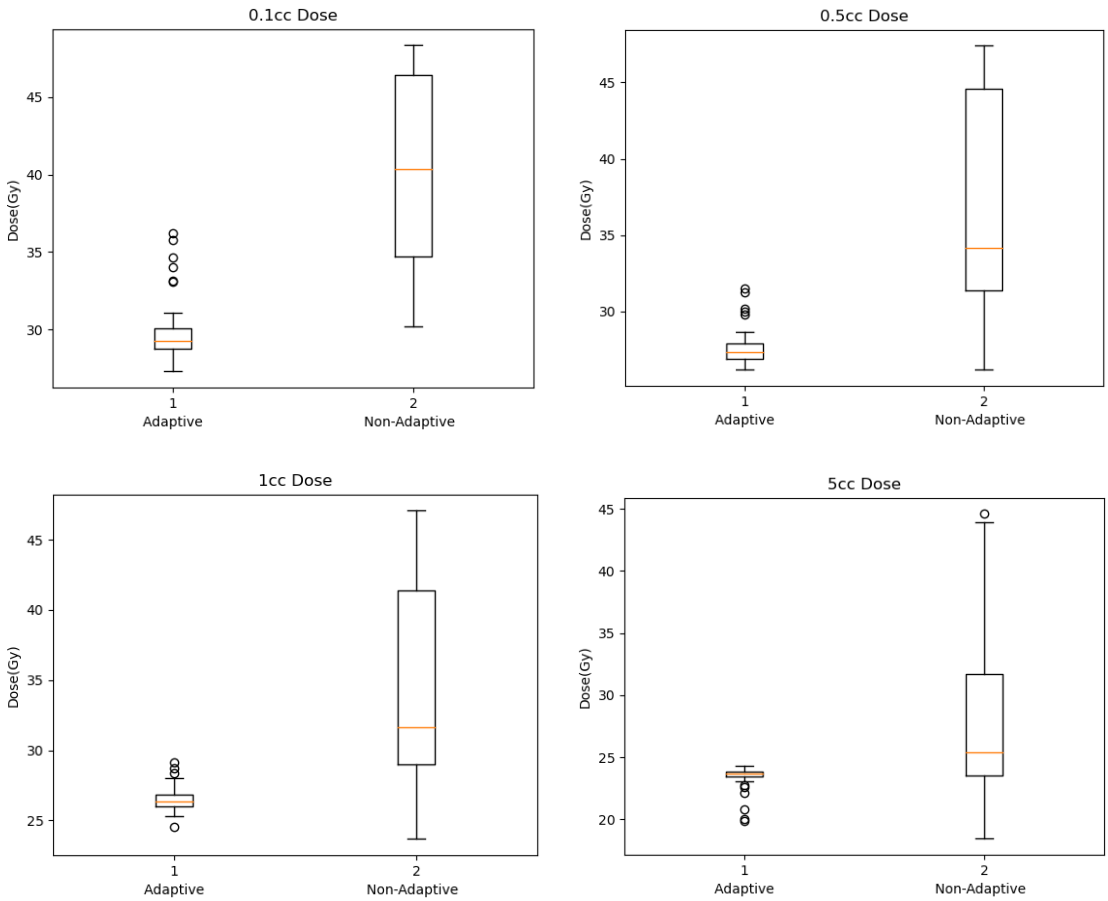
and CT-based imaging to identify a general prognostic phenotype in head-and-neck cancer (51). Building on work that used T2-weighted image-based radiomics to successfully predict response to chemotherapy and radiotherapy (CRT) in Locally Advanced Rectal Cancers (LARCs)(52) , the TRUFI (True Fast Imaging with Steady State Free Precession) imaging provided during MRgRT with the Viewray MR Linac system was used as the basis for a similar study. Being in the class of balanced Steady State Free Precession (bSSFP) sequences, TRUFI (16) uses an unconventional mixed T1/T2 contrast to obtain an image that is robust to motion and flow, and allows continuous imaging without progressive saturation. Nevertheless, TRUFI images obtained at multiple timepoints throughout MRgRT treatment formed the basis of a longitudinal radiomics study that identified a number of features that were predictive of clinical complete response (cCR) in patients undergoing neoadjuvant CRT (53). Deploying such a "delta radiomics" type analysis to the size of patient cohort described here is the next logical step in validating such an approach for clinical use.

This is indeed part of the radiomics procedure; for example, a recent study from the Cleveland Clinic used image-based deep learning for individualisation of radiotherapy dose using information from CT imaging in patients with lung cancer(54). This study is a useful exemplar and shows that in the setting with the best contrast (lung cancer) and using a well-established imaging modality (CT) that pre-treatment images determined through a deep learning algorithm (Deep Profiler) did contain features which were predictive of radiation sensitivity. The study used a large discovery set (849 study patients and a small validation set from other sites in the network, n=95). Similarly, working with Bioengineers and digital pathology we have recently shown that deep learning can enable us to identify robust features in routine H&E histopathology images which link to the underlying gene expression profiles to enable calling of the 4 Consensus Molecular subtypes of colorectal cancer with AUC > 85% in discovery and 2 distinct validation sets totalling 1553 cases (55). This shows our capability to interrogate images using deep learning to identify biological features. Over time, we aim to discover and then validate these biomarkers which will bring together routinely available clinical characteristics such as performance status, co-morbidity and tumour stage and size, with routinely available molecular / pathological data and the imaging data discovered in this project. Ultimately, we aim to identify features which can be captured during the routine care of patients which can be used within algorithms to help inform clinician and patient choices about optimal therapy.

## APPENDIX 4: DOSIMETRIC BENEFIT OF ADAPTIVE RADIOTHERAPY IN PANCREATIC CANCER

Whilst the dosimetric benefit of adaptive radiotherapy in sparing surrounding OAR is well establish internationally in pancreatic cancer we have undergone a local review of patients treated on MRLinac as part of current standard of care service audit to demonstrate this at our local institution and in our patient population. Patients consented for images to be used anonymously for research purposes. DICOM data (MR imaging, structure set and dose cube) from baseline planning and adaptive treatment fractions was anonymised and exported to research server. A locally developed python script was then run on anonymised DICOMs from an initial group of 10 patients. Python script performed 3 functions (1) extraction of dose metrics from baseline plan and adaptive treatment fractions (2) determining a shift vector of baseline structure set to treatment fraction structure set based on a maximisation of volume of GTV overlap, in effect a scripted IGRT match (3) applying determine shift vector to baseline dose cube and extracting dose metrics against the fraction structure set. In this way we extracted clinically delivered adaptive radiotherapy dose metrics and modelled non-adaptive radiotherapy with a scripted IGRT match. Significant dose sparing was seen in clinically delivered adaptive radiotherapy dose metrics compared to modelled non-adaptive radiotherapy. Figure 1 shows volume dose metrics for GI tract from 0.1cc to 20cc volumes. Volume of GI tract receiving a dose of 36Gy, seen as an indicative dose level for risk of grade 3 toxicity, or greater was a median of 0.00cc (0.00-0.1cc) for adaptive radiotherapy and 0.33 cc (0.00-12.7cc) for non-adaptive radiotherapy $p<0.05$.

Sparing of GI tract was achieved without compromise of PTV dose coverage compared to baseline planning; with baseline plan PTV dose to 70% or more of PTV a median of 43.3Gy (42.5-45.3Gy) and adaptive fraction a median of 42.8Gy (40.5-45.4), $p>0.1$.



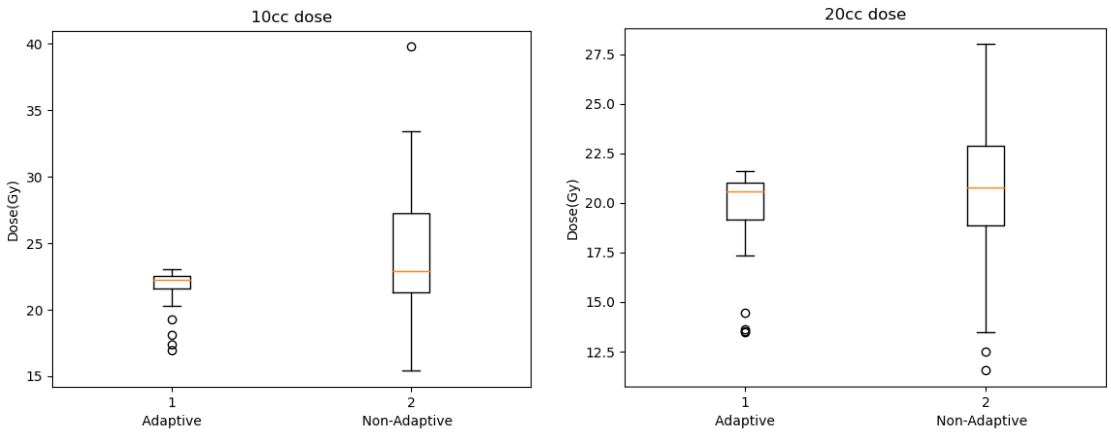



**Figure 1:** GI Tract dose metric (dose to a 0.1-20cc volume) with clinically delivered adaptive radiotherapy and modelled non-adaptive radiotherapy

Modelled isotoxic radiotherapy based on UK SABR consortium mandatory 0.5cc constraint of <35Gy and a local mandatory constraint of 0.1cc<36Gy demonstrated ≥50Gy (100Gy BED) was deliverable to 70% or more of PTV in 6 out of the 10 patients using adaptive radiotherapy. ≥45Gy (BED 85.5Gy) was shown to be deliverable to 9 out of 10 patients using adaptive radiotherapy. Respecting further local constraints of 0.5cc<33Gy and 20cc <25Gy demonstrated ≥50Gy was deliverable in 2 out of the 10 patients, again with ≥45Gy deliverable to 9 out of 10. >50Gy was deliverable in 6 out of 10 patient at a lower coverage of 60% of PTV. This was with simple plan renormalisation by the ratio of constraint to the maximum 0.1cc, 0.5cc and 20cc dose in each patient treatment course without any re-optimisation of treatment plan. Prospective baseline planning and treatment fraction plan adaption to a higher dose prescription would reasonably be expected to further enhance the benefit of adaptive radiotherapy in delivering higher doses whilst maintaining acceptable OAR doses.

## APPENDIX 5: PLANNING FEASIBILITY STUDY OF THREE AND SINGLE FRACTION PANCREAS MR-LINAC SBRT IN PREPARATION FOR A PHASE 1 TRIAL

**Purpose/Objective:** To assess whether three and single fraction Pancreas SBRT can be delivered within defined PTV coverage targets and organs-at-risk (OAR) constraints on an MR-Linac.

**Materials/Methods:**
8 pancreas SABR patients were planned with 39Gy/3# (BED10=90) and 25Gy/1# (BED10=88) with a minimum dose coverage objective of PTV V100%≥60% (CTV=GTV+2mm, PTV=CTV+3mm). OAR constraints were established from national guidelines and published research (see tables). All plans were done on the ViewRay MRIdian® platform (ViewRay®, USA, 2021) using a TRUFI MRI with an accompanying planning CT for electron density information. ~24 IMRT beams were arranged in a pseudo-arc formation avoiding entrance through patients' arms and couch sides. Beam on time and treatment delivery (beam on time plus time for gantry/MLC mechanical motion) time were noted. The impact of a daily non-adaptive workflow was assessed by rigid registration of the plans on the treatment fraction MRIs. Assessment was done following an IGRT match with GTV, PTV and OARs re-contoured to determine the predicted dose if plans were delivered without adaptation on each treatment day.

**Results:**
All plans generated were able to meet the minimum dose coverage objective and OAR constraints (see tables). The median PTV V100 coverage for 39Gy/3# and 25Gy/1# was 75.7% (60.6-91.6%) and 66.1 (60.1-84.2%) respectively. The median treatment delivery times were 15.2min (12.5-21.7min) and 27.8min (21.0-33.2min) for 39Gy/3# and 25Gy/1# respectively.
The predicted doses generated from the treatment fraction MRIs showed potential for PTV under-coverage compared to the planned dose with OARs doses exceeding tolerance, therefore daily adaptive recontouring and planning was essential.

**Conclusion:**
The study results support proceeding with a Phase 1 trial of three and single fraction Pancreas SBRT as all dose coverage and OAR constraints can be met, as well as all treatments can be delivered in a reasonable timeframe. Given that the pancreas is adjacent to radiosensitive OARs and that there is potential for exceeding dose constraints if the treatment is delivered as originally planned, this supports the use of adaptive planning prior to each treatment fraction to ensure that the treatment is delivered safely.

Table 1: Baseline planned PTV coverage, Beam on (BO) times and Treatment delivery (TD) times

| 39Gy/3 # | BO time (min) | TD time (min) | PTV V100% (%) | GTV V100% (%) | 25Gy/1 # | BO time (min) | TD time(min) | PTV V100% (%) | GTV V100% (%) |
|---|---|---|---|---|---|---|---|---|---|
| Max | 15.7 | 21.7 | 91.6 | 99.1 | Max | 26.1 | 33.2 | 84.2 | 92.9 |
| Min | 7.7 | 12.5 | 60.6 | 77.3 | Min | 16.6 | 21.0 | 60.1 | 72.4 |
| Median | 10.5 | 15.2 | 75.7 | 85.1 | Median | 22.8 | 27.8 | 66.1 | 81.2 |

Table 2: Baseline planned volumes for OAR constraints (cc)

| 39Gy/3# | Stomach | | Duodenum | | Small bowel | | Large bowel | |
|---|---|---|---|---|---|---|---|---|
| | ≤0.5cc at 24Gy | ≤5cc at 20Gy | ≤0.5cc at 24Gy | ≤5cc at 20Gy | ≤0.5cc at 24Gy | ≤5cc at 20Gy | ≤0.5cc at 24Gy | ≤5cc at 20Gy |
| Max | 0.5 | 5 | 0.5 | 5 | 0.3 | 3.5 | 0.4 | 5.0 |
| Min | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Median | 0.1 | 3.8 | 0.1 | 3.5 | 0 | 0.9 | 0 | 0.2 |
| **25Gy/1#** | **Stomach** | | **Duodenum** | | **Small bowel** | | **Large bowel** | |
| | ≤0.5cc at 15Gy | ≤5cc at 11Gy | ≤0.5cc at 15Gy | ≤5cc at 11Gy | ≤0.5cc at 15Gy | ≤5cc at 11Gy | ≤0.5cc at 15Gy | ≤5cc at 11Gy |
| Max | 0.1 | 5 | 0.2 | 5 | 0.1 | 4.1 | 0.1 | 5 |
| Min | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Median | 0 | 5 | 0 | 4.2 | 0 | 2.1 | 0 | 0.9 |

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