Evaluation of Hypofractionated Adaptive Radiotherapy using the **MR L**inac in Localise**d** Pancreatic Cancer

Statistical Analysis Plan (SAP)

Data Definitions and Tables

Version 1.0_09Apr2024

Trial Registration: ISRCTN 10557832

Based on Protocol Version 3.0 – 25Sep2023

Oxford Clinical Trials Research Unit (OCTRU)

and

Centre for Statistics in Medicine (CSM)

CONTENTS

1. INTRODUCTION

This document details how the key outcomes for the EMERALD trial will be generated from raw data and reported. This document has been developed in collaboration with the trial team in order to ensure that the data being collected is appropriate, not excessive, and can be reported in a sensible way. The tables and figures are primarily aimed at the final statistical report, funder reports and publications, but may also guide reporting to trial oversight committees.

The EMERALD trial has two distinct parts to the analysis: the final statistical analysis, and trial oversight (interim) analyses which take place during the conduct of the trial. Outcomes collected and analysed in the trial are common to both interim and final analyses, and will be defined in this document. This document will then go on to define the presentation of the final analysis.

2. GENERATION OF OUTCOMES

Data for the trial will be taken from the trial-specific OpenClinica database, which is managed within OCTO. Data downloads are obtained on request from the IT team, via communication with the trial manager.

2.1 Primary outcome

The primary outcome in EMERALD is the Dose Limiting Toxicity (DLT) rate. This rate is calculated using number of occurrences of DLT events (as defined below) in participants taking part in the trial deemed evaluable (numerator), out of the total number of evaluable participants (denominator). An evaluable participant is one who has commenced at least one fraction of radiotherapy.

A DLT event is defined as one of the following events, observed occurring during the DLT observation window defined as the period from starting SBRT treatment to 3 months post-treatment.

- 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)

Different events, or those occurring before or after this defined 3-month observation window will be classed as AEs, but will not constitute a DLT, and will therefore not influence the DLT rate estimate.

Participants who did not complete the 3-month observation window (due to withdrawal/loss-to-follow-up) will still be included in the analysis, assuming they are otherwise evaluable (have received at least one fraction of radiotherapy).

Outcome	*Variable names**	*Time points*	*CRF heading on database*	*Range of possible values & interpretation*	*Scoring instructions (including reference to scoring manual)*
DLT rate	DLT ("Was a DLT identified during this FU?")	CI08 (3 months)	CI095_FU[CI08]	Integer; range 0-1 (binary yes/no outcome)	Set to 'Yes' [1] if one of the following occurs: • 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)

2.2 Secondary Outcome Definitions

Note: The protocol states overall/ progression free survival will be "Defined as the time (date) between registration for this study and death/ progression". The planned analysis will deviate from this definition. These measures will be derived as time from first day of radiotherapy treatment to death/ progression, with appropriate censoring. This is to better align with the standard definitions of Progression free and overall survival. This deviation will be reported in the final statistical report.

Outcome	*Variable names**	*Time points*	*CRF heading on database*	*Range of possible values & interpretation*	*Scoring instructions (including reference to scoring manual)*
Overall survival time from start of radiotherapy	Date_RT_Start ("Date of first fraction") Date_Off_Study ("Last date of study participation") OffStudyReason ("Reason off study") Death_Date ("Date of Death")	CI04 (MR Linac Trt) CI17 (End of Study) CI18 (Death Notification)	CI065_MRgRT[CI04] CI125_End_Of_Study[CI17] CI130_Death_Notification[CI18]	fUpTime_death: count variable – days since RT commenced; integer, ≥0 died: censoring variable (binary yes/no outcome where 0 = NO and 1 = YES); range 0/1	Create 2 derived variables: fUpTime_death: Difference between Date_RT_Start and Date_Off_Study. died: Coded 1 where "OffStudyReason" == EOS008 "Deceased" or date of death is present Replace fUpTime_death: with Death_Date - Date_RT_Start where died == 1
Overall survival time	Date_Diagn ("Date of Diagnosis")	CI01 (Screening)	CI005_Histopath_Diagn[CI01]	fUpTime_death_diag: count variable – days since diagnosis; integer, ≥0	Create 2 derived variables:

from date of diagnosis	Date_Off_Study ("Last date of study participation") OffStudyReason ("Reason off study") Death_Date ("Date of Death")	CI17 (End of Study) CI18 (Death Notification)	CI125_End_Of_Study[CI17] CI130_Death_Notification[CI18]	died: censoring variable (binary yes/no outcome where 0 = NO and 1 = YES); range 0/1	fUpTime_death_diag: Difference between Date_Diagn and Date_Off_Study. died: Coded 1 where "OffStudyReason" == EOS008 "Deceased" or date of death is present Replace fUpTime_death_diag: with Death_Date - Date_Diagn where died == 1
Progression-free survival time from start of radiotherapy	Date_RT_Start ("Date of first fraction") Date_Off_Study ("Last date of study participation") OffStudyReason ("Reason off study") Date_of_Progression ("Date of disease progression")	CI04 (MR Linac Trt) CI17 (End of Study) CI14 (Disease Progression)	CI065_MRgRT[CI04] CI125_End_Of_Study[CI17] CI110_DP[CI14]	fUpTime_progression: count variable – days since RT commenced; integer, ≥0 overallProgression: censoring variable (binary yes/no outcome where 0 = NO and 1 = YES); range 0/1	Create 2 derived variables: fUpTime_progression: Difference between Date_RT_Start and Date_Off_Study. overallProgression: Coded 1 where "OffStudyReason" == EOS006 "Progressive disease" or EOS008 "Deceased" (or date of death/ progression is present), and 0 for all other reasons.

	Death_Date ("Date of Death")	CI18 (Death Notification)	CI130_Death_Notification[CI18]		Replace fUpTime_progression: with Date_of_progress - Date_RT_Start where overallProgression == 1 (and pt progressed) Replace fUpTime_progression: with Death_Date - Date_RT_Start where overallProgression == 1 (and pt died). If pt progressed and died use fUpTime_progression= Date_of_progress - Date_RT_Start where
Progression-free survival time from date of diagnosis	Date_Diagn ("Date of Diagnosis") Date_Off_Study ("Last date of study participation") OffStudyReason ("Reason off study")	CI01 (Screening) CI17 (End of Study)	CI005_Histopath_Diagn[CI01] CI125_End_Of_Study[CI17]	fUpTime_progression_diag: count variable – days since diagnosis; integer, ≥0 overallProgression: censoring variable (binary yes/no outcome where 0 = NO and 1 = YES); range 0/1	Create 2 derived variables: fUpTime_progression_diag: Difference between Date_RT_Start and Date_Off_Study. overallProgression: Coded 1 where "OffStudyReason" == EOS006 "Progressive disease" or EOS008 "Deceased" (or date of

	Date_of_Progression ("Date of disease progression") Death_Date ("Date of Death")	CI14 (Disease Progression) CI18 (Death Notification)	CI110_DP[CI14] CI130_Death_Notification[CI18]		death/ progression is present), and 0 for all other reasons. Replace fUpTime_progression_diag: with Date_of_progress – Date_Diagn where overallProgression == 1 (and pt progressed) Replace fUpTime_progression_diag: with Death_Date – Date_Diagn where overallProgression == 1 (and pt died). If pt progressed and died use fUpTime_progression= Date_of_progress – Date_Diagn where
Local progression survival time from start of radiotherapy	Date_RT_Start ("Date of first fraction") OffStudyReason ("Reason off study")	CI04 (MR Linac Trt) CI17 (End of Study)	CI065_MRgRT[CI04] CI125_End_Of_Study[CI17]	fUpTime: count variable – days since RT commenced; integer, ≥0 localProgression: censoring variable (binary yes/no outcome where 0 = NO and 1 = YES to indicate that either	Create 2 derived variables: fUpTime_localProgression: Difference between Date_RT_Start and either Date_Off_Study (if either died or no local progression,

	Date_of_Progression (“Date of progression”) SitesOfDisProgression (“Sites of disease progression”) Death_Date (“Date of Death”)	CI14 (Disease Progression) CI18 (Death Notification)	CI110_DP[CI14] CI130_Death_Notification[CI18]	local progression, progression or death has been observed); range 0/1	progression or death observed or (in order of preference): difference between Date_RT_Start and Date_of_Progression if loco-regional progression observed (i.e. SitesOfDisProgression == Local progression within the primary tumour) difference between Date_RT_Start and Date_of_Progression if no loco-regional progression observed (i.e. SitesOfDisProgression != Local progression within the primary tumour) difference between Date_RT_Start and Death_Date if no loco-regional progression observed and no progression localProgression: Coded 1 where “OffStudyReason” ==

					EOS008 “Deceased” OR SitesOfDisProgression == 1 “Local progression within the primary tumour”, and 0 otherwise OR patient progressed (date of progression present)
Local progression survival time from date of diagnosis	Date_Diagn (“Date of Diagnosis”) OffStudyReason (“Reason off study”) Date_of_Progression (“Date of progression”) SitesOfDisProgression (“Sites of disease progression”) Death_Date (“Date of Death”)	CI01 (Screening) CI17 (End of Study) CI14 (Disease Progression) CI18 (Death Notification)	CI005_Histopath_Diagn[CI01] CI125_End_Of_Study[CI17] CI110_DP[CI14] CI130_Death_Notification[CI18]	fUpTime_localProgression_diag: count variable – days since diagnosis; integer, ≥0 localProgression: censoring variable (binary yes/no outcome where 0 = NO and 1 = YES to indicate that either local progression, progression or death has been observed); range 0/1	Create 2 derived variables: fUpTime_localProgression_diag: Difference between Date_Diagn and either Date_Off_Study (if either died or no local progression, progression or death observed or (in order of preference): difference between Date_Diagn and Date_of_Progression if loco-regional progression observed (i.e. SitesOfDisProgression == Local progression within the primary tumour) difference between Date_Diagn and Date_of_Progression if no

					loco-regional progression observed (i.e. SitesOfDisProgression != Local progression within the primary tumour) difference between Date_Diagn and Death_Date if no loco-regional progression observed and no progression localProgression: Coded 1 where "OffStudyReason" == EOS008 "Deceased" OR SitesOfDisProgression == 1 "Local progression within the primary tumour", and 0 otherwise OR patient progressed (date of progression present)
Overall resection Rate (for those undergoing surgery)	Tumor_Resection ("Was surgical resection of the target tumour attempted?") Resected_Tumour ("Was the tumour resected?")	CI12 (Post-RT Surgery)	CI105_Surgery	Resected_Tumour: Binary yes/no outcome where 0 = NO and 1 = YES to indicate that the tumour has been successfully resected); range 0/1	Derive number of resected tumours out of i) total participants ii) those tumour resection attempted.

Resection Margin Rate (for those undergoing surgery)	Resected_Tumour ("Was the tumour resected?") Resection_Margin ("Resection Margin")	CI12 (Post-RT Surgery)	CI105_Surgery	Resection Margin: Categorical outcome where 0 = "R0"; 1 = "R1"; 2 = "R2"	Derive number of resected tumours out of i) total participants ii) those with resected tumours (i.e. Resected_Tumour == YES)
Complete response rate (for those undergoing surgery)	Resected_Tumour ("Was the tumour resected?") CT_Response ("Disease response (radiologist's interpretation)")	CI12 (Post-RT Surgery) CI08 (3 months) CI09 (6 months) CI10 (12 months) CI14 (Disease progression) CI19 (Additional Assessments)	CI105_Surgery[CI12] CI075_Restaging_Scan[CI08;CI09; CI10; CI14;CI19]	Resected_Tumour: Binary yes/no outcome where 0 = NO and 1 = YES to indicate that the tumour has been successfully resected); range 0/1 CT_Response categorical variable with options: Response, Stable disease, Progressive disease	Describe the CT_response rates for those individuals that had a resection only (i.e. where Resected_Tumour == YES).
Late Gastrointestinal or other	AE (Adverse Event Name (NOTE: during final analysis report	3-24 months	CI090 AEs	N/A report all late onset toxicities with emphasis on events with CTCAE grade > 2.	Describe the late onset adverse events for those individuals that had a resection only (i.e. where

Adverse Events	MedDRA Coded Event Names)) StartDate (Date when adverse event started) StopDate (Date of resolution of the adverse event; otherwise it is the date of change of CTCAE grade) CTCAE_Grade MRgRT_causality SAE DLT (DLT? (related to SBRT within 3 months from start of MRgRT)) RT_Late_Toxicity (Late-onset severe MRgRT toxicity (i.e. related to MRgRT and > 3 months from start of MRgRT until the end of the trial)?) AEOutcome				"Late-onset severe MRgRT toxicity (i.e. related to MRgRT and > 3 months from start of MRgRT until the end of the trial)?" variable is "Yes).
Freedom from further line	Date_RT_Start	CI04 (MR Linac Trt)	CI065_MRgRT[CI04]	fUpTime_furtherLineChemo: count variable – days from	Create 1 derived variable:

chemotherapy: time from completion of RT to start of further chemotherapy	("Date of first fraction") Further_Chemo ("Has the patient received any chemotherapy post MRgRT for the cancer under study?") Date_Start_postChemo ("Start date")	CI13 (Post RT Chemotherapy)	CI100_ChemoPostRT[CI13]	RT commenced until further chemo commenced; integer, ≥0 Further_Chemo: (binary yes/no outcome where 0 = NO and 1 = YES to indicate that either further post-MRgRT chemotherapy has commenced); range 0/1. fUpTime_furtherLineChemo only possible to be derived if Further_Chemo==1.	fUpTime_ furtherLineChemo: Difference between Date_RT_Start and Date_Start_postChemo

3. DEFINITIONS OF ANALYSIS POPULATION

Primary Safety Population:

All patients enrolled in the study and who received at least one dose of MRgRT, irrespective of withdrawal status.

Sensitivity Population:

All patients in the primary population, excluding those for whom plans generated did not meet the dose constraints for their allocated regimen. These patients will be identified by a discrepancy between the "Patient will be involved in" question from the CI000_reg CRF and the "Fractionation" question from CI065_MRgRT CRF. This discrepancy indicates that the patient was switched to a higher fraction regimen than what was initially allocated to them due to not meeting dose constraints.

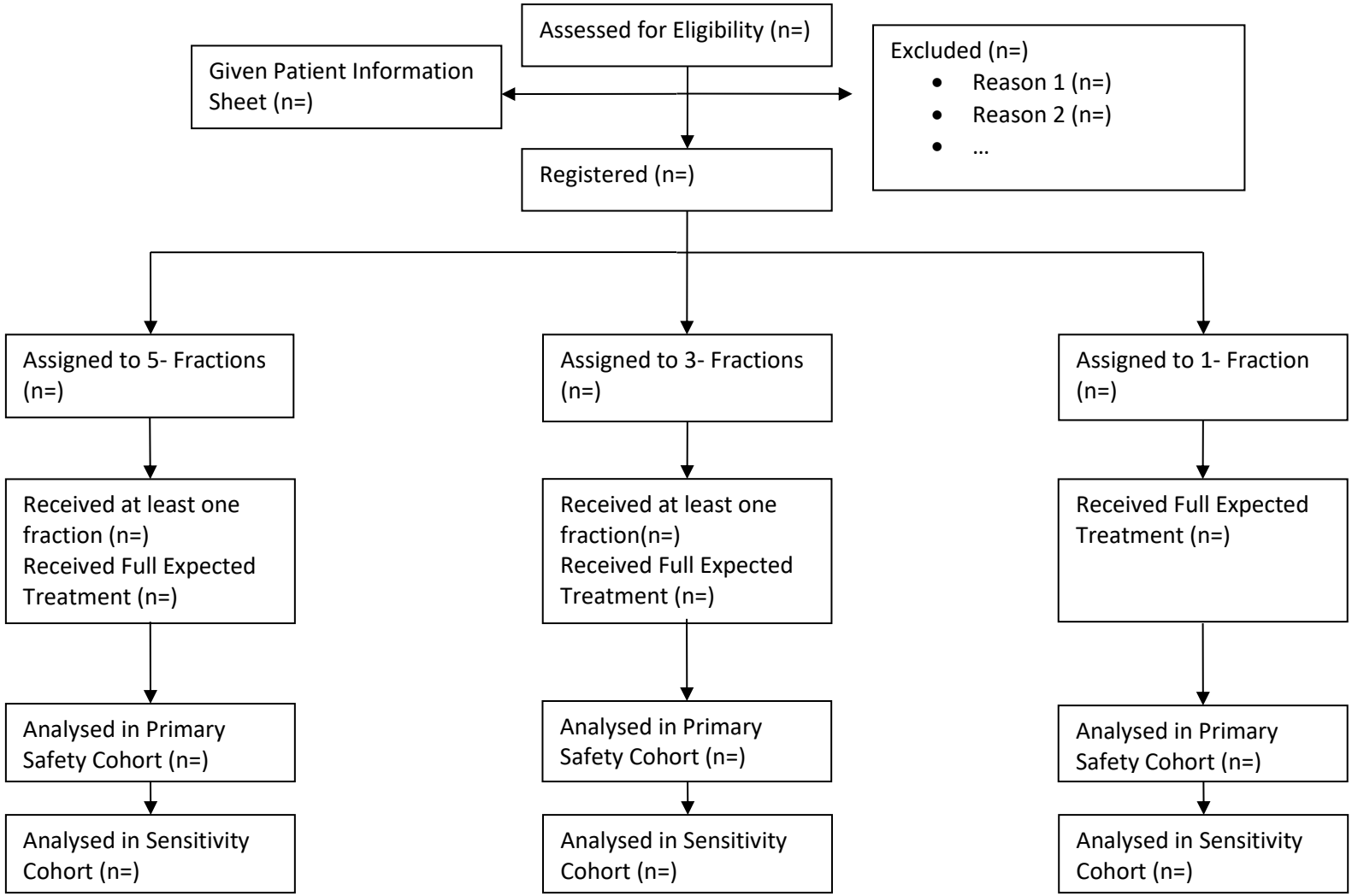
Data will be presented based on the primary safety population for each treatment cohort, unless otherwise stated.

4. PRESENTATION OF KEY TRIAL DATA

***Note**: Tables are presented giving Mean (SD), this can be changed in the analyses to Median (IQR), Median (Range), or any combination of these statistics (or all three) as appropriate. Headings in this document are illustrative.*

***Note:** Any data presented in the final statistical report may also be presented visually to aid interpretation. Possible dummy figures will not be presented in this document.*

4.1 CONSORT flow diagram


Assessed for Eligibility (n=)
Given Patient Information Sheet (n=)
Excluded (n=)
Reason 1 (n=)
Reason 2 (n=)
…
Registered (n=)
Assigned to 5- Fractions (n=)
Assigned to 3- Fractions (n=)
Assigned to 1- Fraction (n=)
Received at least one fraction (n=)
Received Full Expected Treatment (n=)
Received at least one fraction(n=)
Received Full Expected Treatment (n=)
Received Full Expected Treatment (n=)
Analysed in Primary Safety Cohort (n=)
Analysed in Primary Safety Cohort (n=)
Analysed in Primary Safety Cohort (n=)
Analysed in Sensitivity Cohort (n=)
Analysed in Sensitivity Cohort (n=)
Analysed in Sensitivity Cohort (n=)

4.2 Patient withdrawal

Table 1: Patient withdrawal or loss to follow-up

Patient	Fractionation Regimen	Withdrawal type[1]	Withdrawal timepoint[1]	Time in Study[2,3]	Reason off study[3]
		Consent withdrawal/Loss to FU/Death/Other	Before treatment/during planning scan/during MRgRT treatment/post DLT period		

[1]CI095_FU, [2]CI100_Registration, [3]CI125_End_Of_Study

4.3 Baseline characteristics

Table 2: Baseline characteristics

	5-Fractions (n=)	3-Fractions (n=)	1-Fraction (n=)	Total (n=)
Age[1]				
Time since Diagnosis (Years) [2]				
Sex[1]				
Male				
Female				
Carcinoma Diagnosis Confirmation Method[2]				
Histologically				
Cytologically				
MDT confirmed				
Diameter of Target lesion (mm)[3,10]				
Standardised uptake value (SUV) of target lesion[3]				
Site of Target Tumour Within Pancreas[3]				
Head				
Body or Tail				
Other Tumour Bed Recurrence				
Nodal Recurrence				
Tumour Resectability[3]				
Resectable				
Borderline Resectable				
Resectable but Medically Inoperable				
Unresectable				
Previous Chemotherapy?[5]				
Yes				
No				

	5-Fractions (n=)	3-Fractions (n=)	1-Fraction (n=)	Total (n=)
Previous Chemotherapy Response[5]				
Responded				
Stable				
Local Progression				
No Previous Chemotherapy				
Number of Previous Chemotherapy Lines Received[5]				
Latest Line of Previous Chemotherapy[5]				
Gemcitabine				
Gemcitabine and Capecitabine (or 5FU)				
Oxaliplatin and Capecitabine (or 5FU)				
FOLFIRINOX (5FU, Oxaliplatin, Irinotecan, Folinic Acid)				
Irinotecan and 5FU (or Capecitabine)				
Other				
No Previous Chemotherapy				
CA 19-9 (U/mL)[8]				
ECOG Performance Status[9]				
0				
1				
2				
3				
4				

[1]CI000_Registration, [2]CI005_Histopath_Diagn, [3]CI010_Baseline_Scan, [4]CI015_PMH_&_BSS, [5]CI020_Prior_Chemo, [6]CI025_Scr_Haem, [7]CI030_Scr_Bioch, [8]CI035_CA19_9, [9]CI045_Scr_PS
[10]The largest diameter recorded from CT-scan, MRI scan and/or FDG PET-CT scan.
Summaries are presented as Mean (SD) for continuous outcomes or n (%) for categorical outcomes.

Table 3: Baseline signs and symptoms

Subject	Fractionation Regimen	Signs and Symptoms[1]	Date of onset[1]	CTCAE grade[1]

[1]CI015_PMH_&_BSS
If there are multiple of the same Signs and Symptoms, it may be appropriate to present this data in a summary table as well as the line listing. It may also be useful to present frequency plots of each Sign/ Symptom by Grade and/ or Fractionation Regimen.

4.4 Treatment compliance & details of the interventions

All compliance data is taken from CI065_MRgRT CRF apart from Table 6 which is non-CRF data and will be provided by study clinicians after review.

Table 4: Treatment compliance summary

	5-Fractions (n=)	3-Fractions (n=)	1-Fraction (n=)	Total (n=)
% Planned MRgRT received				
Full Planned MRgRT Dose Given				
Yes				
No				
Missed Doses of Planned MRgRT				
Yes				
No				
Treatment Time Per Fraction (Minutes)				
Treatment Stopped Early				
Yes				
No				
Treatment Stopped Early Reason				
Disease progression				
Unexpected Toxicity				
AE/SAEs requiring discontinuation				
Clinical decision				
Patient decision				
Significant protocol deviation or inability to comply with trial procedures				
Pregnancy				
Patient Consent Withdrawal				
Treatment never started				
Other				

Table 5: Treatment compliance per participant

Subject	Intended Fractions	Fractions Delivered	Total Dose Delivered (Gy)	Additional Fractions Received	Missed Fractions	Mean Treatment Time per Fraction (Minutes)

Table 6: Details of MRgRT delivered

	N	PTV V (100%) % Mean (Min, Max)			PTV High V (95%) % Mean (Min, Max)			GTV (cc) Mean (Min, Max)		PTV (cc) Mean (Min, Max)	
		Baseline	Predicted	Reoptimised	Baseline	Predicted	Reoptimised	Baseline	Adapted	Baseline	Adapted
5-Fractions											
3-Fractions											
1-Fraction											

Non-CRF data and summaries will be provided by study clinicians after review.

Plots of fraction treatment time for each participant, by fractionation regimen, and of % Planned MRgRT received for each participant, marking different treatment regimens will also be included. Further data visualisation will be explored.

4.5 Trial Results

Note: Each Regimen is analysed as independent cohorts and no between cohort comparison is intended.

4.5.1 Primary outcome

Primary analysis will be performed using a **prior distribution of Beta(1,7)** for each dose regimen. This prior will also be used as the prior for the primary analysis in each Safety TMG.

Table 7: Results of primary analysis

Fractionation Regimen	Number of Patients Included in Primary Analysis	Number of Dose Limiting Toxicities Observed	Observed DLT Rate	Regimen Safe (regimen considered safe if it did not stop early due to safety*)?	Overdose Probability	95% Credible Interval**
5-Fractions						
3-Fractions						
1-Fraction						

**Stop early for safety if P(risk of DLT > 0.15 | Regimen, Data) > 0.8, i.e., the probability that the true DLT rate in a given regimen is unsafe (above 15%) is above 0.8 based on our prior belief and the data observed.*
***95% chance that the true toxicity rate for each regimen is in this interval.*
CI070_DLT_Assessment

Plots of the final posterior distribution of DLT rate for each regimen will be presented, delineating between the "Safe" and "Unsafe" areas of this distribution (i.e. <15% and >15%). Visual representations of DLTs by regimen or participant may also be presented.

4.5.2 Sensitivity Analyses

Primary outcome tables and figures will be repeated in all fractionations for:

- Sensitivity population
- Primary safety population, with a Beta(1,3) prior
- Primary safety population, with a Beta(1,1) prior.

4.5.3 Secondary outcomes

4.5.3.1 Overall Survival

Overall survival (OS) will be presented as Kaplan-Meier and swimmer plots for each regimen separately. Kaplan-Meier plots will present numbers at risk over time. OS at one year and median OS will be reported.

Table 8: Overall survival at 12 and 24 months

	5-Fractions (n=)		**3-Fractions (n=)**		**1-Fraction (n=)**		**Total (n=)**	
	Event/ n	Survival rate	Event/ n	Survival rate	Event/ n	Survival rate	Event/ n	Survival rate
12 months overall survival from start of RT								
12 months overall survival from date of diagnosis								
24 months overall survival from start of RT								
24 months overall survival from date of diagnosis								

Table 9: Summary of deaths during study

Subject	**Fractionation Regimen**	**Overall Survival Time from start of RT (Days)**	**Overall Survival Time from date of diagnosis (Days)**	**Cause of Death**

CI130_Death_Notification, CI115_PSU

If appropriate (there are sufficient events, to be determined after final data lock, for this to be meaningful), deaths will be presented in a summary table summarising cause of death and overall survival time.

4.5.3.2 Progression Free Survival

Progression free survival (PFS) will be presented as Kaplan-Meier and swimmer plots for each regimen separately. Kaplan-Meier plots will present numbers at risk over time. PFS at one year and median PFS will be reported.

Table 10: Progression free survival at 12 and 24 months

	5-Fractions (n=)	**3-Fractions (n=)**	**1-Fraction (n=)**	**Total (n=)**

	Event/ n	Survival rate	Event/ n	Survival rate	Event/ n	Survival rate	Event/ n	Survival rate
12 months progression free survival from start of RT								
12 months progression free survival from date of diagnosis								
24 months progression free survival from start of RT								
24 months progression free survival from date of diagnosis								

Table 11: Summary of disease progression

	5-Fractions (n=)	**3-Fractions (n=)**	**1-Fraction (n=)**	**Total (n=)**
Disease Progression				
Yes				
No				
Progression Diagnosis Method				
Clinical Examination				
CT/ MRI/ FDG PET Scan				
CA19-9				
Other				
Did Not Progress				
Progression Site (Possible to Progress in Multiple Sites)				
Local progression within the primary tumour				
Loco-regional progression with new lesions outside the primary tumour				
Distant metastases				
Did Not Progress				
Distant metastases Site (Possible to have Multiple)				
Liver				
Lung				
Peritoneum				
Other				
No Distant Metastases				

CI110_DP

4.5.3.3 Local Progression Free Survival

Local PFS will be presented as Kaplan-Meier and swimmer plots for each regimen separately. Kaplan-Meier plots will present numbers at risk over time. Local PFS at one year and median local PFS will be reported.

Table 12: Local progression free survival at 12 and 24 months

	5-Fractions (n=)		**3-Fractions (n=)**		**1-Fraction (n=)**		**Total (n=)**	
	Event/ n	Survival rate	Event/ n	Survival rate	Event/ n	Survival rate	Event/ n	Survival rate
12 months local progression free survival from start of RT								
12 months local progression free survival from date of diagnosis								
24 months local progression free survival from start of RT								
24 months local progression free survival from date of diagnosis								

4.5.3.4 Surgical Outcomes

Table 13: Surgical outcomes summary

	5-Fractions (n=)	**3-Fractions (n=)**	**1-Fraction (n=)**	**Total (n=)**
Surgical Resection Attempted[1]				
Yes				
No				
Disease Response[2]				
Response				
Stable Disease				
Progressive Disease				

[1]CI105_Surgery, [2]CI075_Restaging_Scan at 3 months

Table 14: Summary of surgical tumour resection

	5-Fractions (n=)	3-Fractions (n=)	1-Fraction (n=)	Total (n=)
Surgical Procedure				
Curative pancreatico-duodenectomy				
Palliative bypass surgery				
Just open and close the abdomen				
Other				
Tumour Resected				
Yes				
No				
Tumour Type				
Adenocarcinoma				
Other				
Tumour Grade/ Differentiation				
1				
2				
3				
Unknown/Undifferentiated				
Resection Margin				
R0				
R1				
R2				
Lymphovascular Invasion				
Present				
Absent				
Not Available				
Perineural invasion				
Present				
Absent				
Not Available				
T Staging				
T0				
T1				
T2				
T3				
T4				
Tx				

CI105_Surgery

Percentages are out of the number of participants for whom surgical resection was attempted, presented in Table 13.

4.5.3.5 Toxicity

This secondary outcome is covered by Section 4.6.

4.5.3.6 Freedom from further chemotherapy

Time from completion of Radiotherapy to start of further chemotherapy will be presented in a Kaplan-Meier plot for each regimen.

Table 15: Summary of post-MRgRT chemotherapy received

	5-Fractions (n=)	3-Fractions (n=)	1-Fraction (n=)	Total (n=)
Post-MRgRT Chemotherapy[1]				
Yes				
No				
Regimen				
Gemcitabine				
Gemcitabine and Capecitabine (or 5FU)				
Oxaliplatin and Capecitabine (or 5FU)				
FOLFIRINOX (5FU, Oxaliplatin, Irinotecan, Folinic Acid)				
Irinotecan and 5FU (or Capecitabine)				
Other				
Did not have Post-MRgRT Chemotherapy				
Intent				
Adjuvant/maintenance				
Palliative				
Did not have Post-MRgRT Chemotherapy				
Time from Completion of Radiotherapy to Start of Further Chemotherapy (Days)[2]				

[1]CI095_FU, [2]Derived variable across multiple CRFs, see 2.2 for details.

Post MRgRT Chemotherapy Listing (Note: this data may be "long" as patients may start multiple Chemotherapy Regimens)

Table 16: Post-MRgRT chemotherapy per participant

Subject	Post MRgRT Chemotherapy Regimen	Time from Completion of Radiotherapy to Start of Chemotherapy (Days)	Treatment Intent

CI100_Chemo_Post_MRgRT

4.6 Safety

For the final statistical report, use the MedDRA coded event names and organ classes. During the trial for interim analyses, use the names given on CI090_AEs CRF.

Bar plots of adverse events by relatedness, grade and regimen will be presented. The proportion of patients exhibiting each Adverse Event will be presented visually. The maximum grade Adverse Event for each patient will be presented graphically by treatment regimen.

Adverse events table will be presented twice, for two sets of events:

1) All Adverse Events recorded throughout the trial
2) Late onset (> 3 months after starting treatment) subset of Adverse Events.

Table 17: Dose limiting toxicities

Subject	Fractionation Regimen	Description	CTCAE Grade	RT causality	MRI Causality	Outcome	Time to Resolve (Days)

CI090_AEs

Table 18: Serious adverse events

Subject	Fractionation Regimen	Description	CTCAE Grade	RT causality	MRI Causality	Late Onset	Outcome	Time to Resolve (Days)

CI090_AEs

Table 19: Adverse event summary

	5-Fractions (n=)	3-Fractions (n=)	1-Fraction (n=)	Total (n=)
Number of Adverse Events				
Number of Adverse Events CTCAE Grade 3+				
Adverse Events per Patient				
CTCAE Grade				
1				
2				
3				
4				
5				
Relatedness				
Definitely Related				
Probably Related				
Possibly Related				
Probably Not Related				
Definitely Not Related				
Time to Resolve (Days)[1]				
Late-onset severe MRgRT toxicity				
Yes				

No				
N/A				

CI090_AEs

[1]Summaries given in mean (SD) or median (IQR).

Adverse Events by MedDRA Organ Class and MedDRA Coding (With EXAMPLE Classes and Coding)

	5-Fractions (n=)	**3-Fractions (n=)**	**1-Fraction (n=)**	**Total (n=)**
MedDRA Organ Class				
Blood & Lymphatic System Disorders				
Eye Disorders				
…				
MedDRA Coding				
Abdominal Pain Upper				
Anaemia				
…				

5. OTHER

Exploratory outcomes:

- Imaging and blood assessments
- Additional 0.35T MR imaging post fractions and research bloods

Other Data that will be reported in the final statistical report:

- Restaging Scans (CI075_Restaging_Scan)
- ECOG Performance Status over time (CI060_PS)
- CA19.9 over time (CI035_CA19_9)

Table 20: Summary results of Restaging Scans – 3 Months

	5-Fractions (n=)	**3-Fractions (n=)**	**1-Fraction (n=)**	**Total (n=)**
	n (%)	**n (%)**	**n (%)**	**n (%)**
Restaging Scan Taken				
Yes				
No				
Diameter of target lesion (mm)[1,2]				
Second target lesion identified by CT, MRI or FDG PET-CT Scan				
Yes				
No				
Scans not taken				
New lesions identified				
Yes				
No				

	5-Fractions (n=)	3-Fractions (n=)	1-Fraction (n=)	Total (n=)
	n (%)	n (%)	n (%)	n (%)
Scans not taken				
Disease response				
Response				
Stable disease				
Progressive disease				
Scans not taken				
Tumour resectable				
Yes				
No				
Resectability not assessed				
Scans not taken				
Metastatic regional lymph nodes detected				
Yes				
No				
Cannot be assessed				
Scans not taken				
TNM staging post MRgRT done				
Yes				
No				
Cannot be assessed				
Scans not taken				
T staging				
T0				
T1				
T2				
T3				
T4				
Tx				
Scans not taken				
N staging				
N0				
N1				
NX				
Scans not taken				
M staging				
M0				
M1				
Scans not taken				

CI075_Restaging_Scan

[1]*Summaries given in mean (SD) or median (IQR).*

[2]*The largest diameter recorded from CT-scan, MRI scan and/or FDG PET-CT scan.*

Note: Table 20 can be duplicated for other re-staging scan timepoints (6 months, 18 months) if required.

Table 21: Summary of ECOG performance status over time

	5-Fractions (n=)	3-Fractions (n=)	1-Fraction (n=)	Total (n=)
	n (%)	n (%)	n (%)	n (%)
Baseline (at screening)				
0				
1				
2				
3				
4				
Not measured				
Prior to MR Linac treatment				
0				
1				
2				
3				
4				
Not measured				
Week 1 post-treatment				
0				
1				
2				
3				
4				
Not measured				
6 weeks from start of RT				
0				
1				
2				
3				
4				
Not measured				
3 months from start of RT				
0				
1				
2				
3				
4				
Not measured				
6 months from start of RT				
0				
1				
2				
3				
4				
Not measured				

	5-Fractions (n=)	3-Fractions (n=)	1-Fraction (n=)	Total (n=)
	n (%)	n (%)	n (%)	n (%)
12 months from start of RT				
0				
1				
2				
3				
4				
Not measured				
18 months from start of RT				
0				
1				
2				
3				
4				
Not measured				
24 months from start of RT				
0				
1				
2				
3				
4				
Not measured				

CI045_Scr_PS, CI060_PS

Table 22: Summary of CA19.9 blood marker over time

	5-Fractions (n=)	3-Fractions (n=)	1-Fraction (n=)	Total (n=)
CA19.9 (U/ mL)	**n, mean (SD), min, max**	**n, mean (SD), min, max**	**n, mean (SD), min, max**	**n, mean (SD), min, max**
Baseline				
3 weeks from start of RT				
3 months from start of RT				

CI035_CA19_9

Disease response (from *CI075_Restaging_Scan*), performance status and CA19.9 levels will be explored via visual representations of the data over time, and if suitable these visualisations will be presented in the final statistical report.

6. GLOSSARY OF ABBREVIATIONS

EMERALD	**E**valuation of Hypofractionated Adaptive Radiotherapy using the **MR** **L**inac in Localise**d** Pancreatic Cancer
OCTO	**O**ncology **C**linical **T**rials **O**ffice
OCTRU	**O**xford **C**linical **T**rials **R**esearch **U**nit
DLT	**D**ose **L**imiting **T**oxicity
CTCAE	**C**ommon **T**erminology **C**riteria for **A**dverse **E**vents
RECIST	**R**esponse **E**valuation **C**riteria in **S**olid **T**umours
AE	**A**dverse **E**vent
SAE	**S**erious **A**dverse **E**vent
PFS	**P**rogression-**f**ree **S**urvival
OS	**O**verall **S**urvival
SABR/SBRT	**S**tereotactic (**a**blative) **b**ody **r**adio**t**herapy
CONSORT	**Con**solidated **S**tandards **o**f **R**eporting **T**rials
MRgRT	**M**agnetic **R**esonance **g**uided **R**adio**T**herapy