



## Ultra-hypofractionated radiotherapy to the stellate ganglia for ventricular arrhythmia using MR-guided radiotherapy

### Pre-trial commissioning

**Dr Ben George**

Principal Physicist for MR-Linac Service Development  
GenesisCare UK



**NHS**  
Oxford University Hospitals  
NHS Foundation Trust

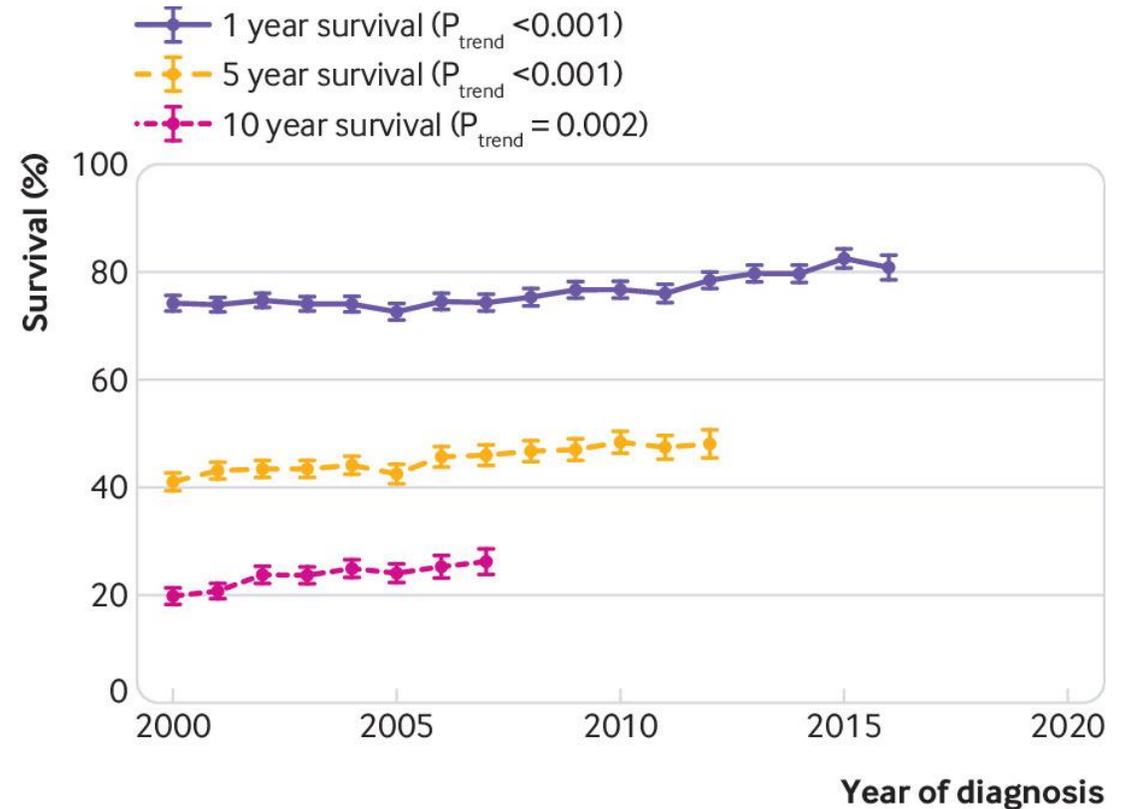


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**OXFORD**

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# Ventricular arrhythmia

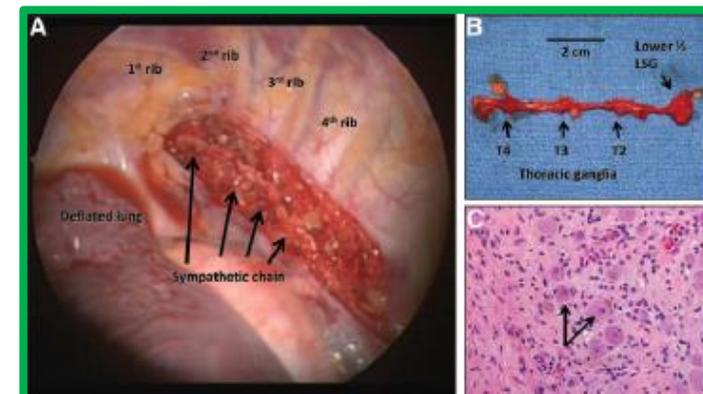
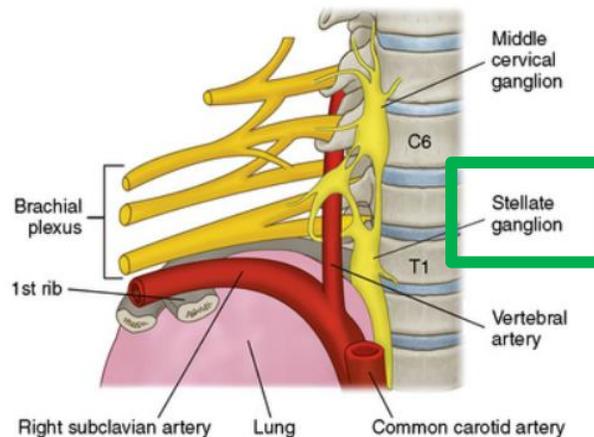
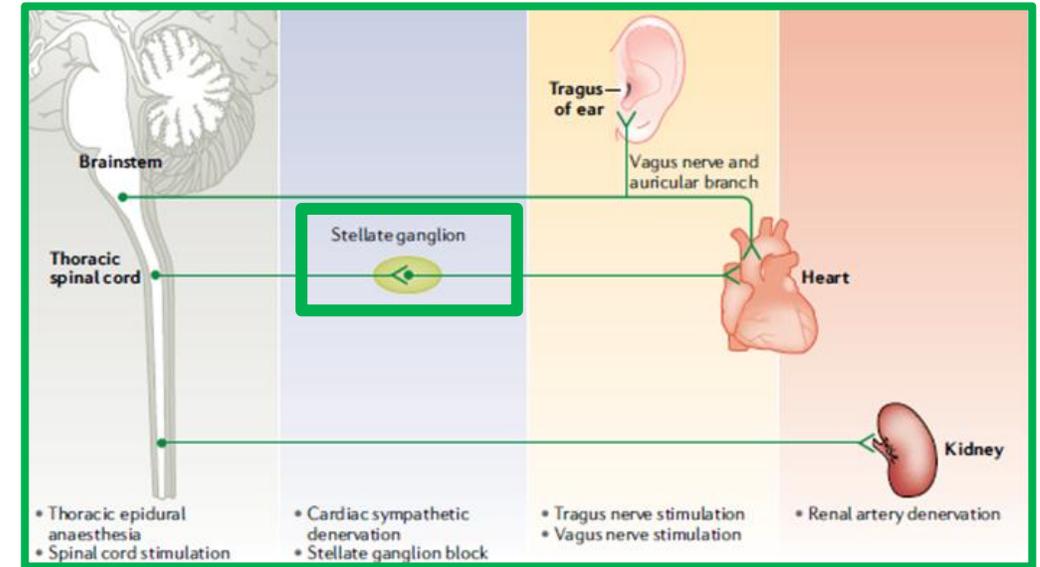
- ⑦ Over 1 million people living with heart failure in UK
  - ⑦ 200,000 new diagnoses per year
  - ⑦ Survival after diagnosis has steadily improved over time
  - ⑦ 5-year mortality around 50%
- ⑦ Ventricular arrhythmias are the most common cause of sudden cardiac death
- ⑦ Most ventricular arrhythmias are triggered by the sympathetic nervous system via the stellate ganglia



- Taylor CJ, Ordóñez-Mena JM, Roalfe AK, Lay-Flurrie S, Jones NR, Marshall T, Hobbs FR. Trends in survival after a diagnosis of heart failure in the United Kingdom 2000-2017: population based cohort study. *bmj*. 2019 Feb 13;364.
- Shen L, Jhund PS, Petrie MC, Claggett BL, Barlera S, Cleland JG, Dargie HJ, Granger CB, Kjekshus J, Køber L, Latini R. Declining risk of sudden death in heart failure. *New England Journal of Medicine*. 2017 Jul 6;377(1):41-51.

# Stellate ganglion and ventricular arrhythmias

- ⑦ Stellate ganglion is a cluster of sympathetic nerves either side of the lower neck, above the clavicle
- ⑦ Part of the sympathetic nervous system, overactivity can contribute to ventricular arrhythmias
- ⑦ Partial surgical removal of stellate ganglia is an option in some patients with proven benefit
- ⑦ Whether radiotherapy can be targeted at the stellate ganglia to reduce arrhythmia is unknown



- Herring N, Kalla M, Paterson DJ. The autonomic nervous system and cardiac arrhythmias: current concepts and emerging therapies. *Nature Reviews Cardiology*. 2019 Dec;16(12):707-26.
- <https://neupsykey.com/sympathetic-nerve-block-and-neurolysis>

# RADIO STAR: Magnetic resonance guided stereotactic radiotherapy to the stellate ganglia for ventricular arrhythmia

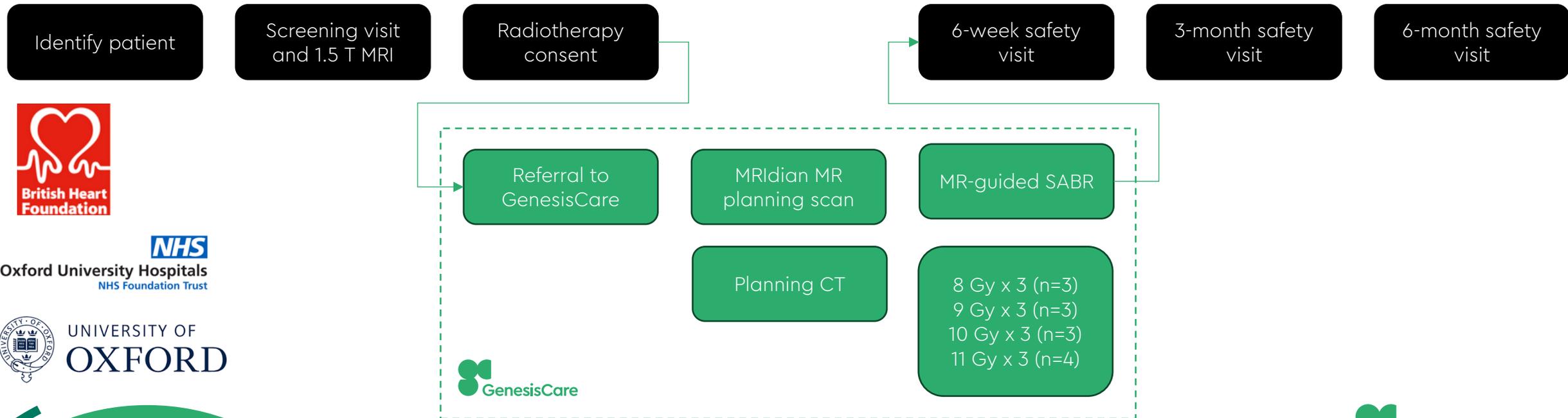
## Phase I clinical trial

### Primary objective

- ⑦ Safety of MR-guided radiotherapy to modify the stellate ganglia

### Secondary objectives

- ⑦ Assess anatomical and functional changes (MR, haemodynamic, biomarker levels, VT episodes, PROMs)



# Clinical trial governance

**GenesisCare is delivering a service for this trial – IRAS, ethics, etc. sits with the trial sponsor and recruiting site.**

**Delivering a new clinical service requires approval and governance in place. If GenesisCare were a sponsor, then the IRAS form would provide all the evidence**

- ⑦ Identify lead Practitioner and MPE for implementation within GenesisCare
- ⑦ Gather minimum trial dataset for review
  - ⑦ IRAS form, trial protocol, ethics approval, sponsor letter approving opening of trial, funding agreements (as required)
- ⑦ Review trial protocol and identify any changes in local practice to be implemented
- ⑦ Create GenesisCare Radiotherapy Guidance document to cover trial activities
  - ⑦ Highlight deviations from standard practice
  - ⑦ Identify any additional training requirements
- ⑦ Training and briefing with local teams
- ⑦ Go/no-go call with service leads before accepting first referral

# Radiotherapy guidance document

**RT-SOP-607**  
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## MR-guided Radiotherapy to the Stellate Ganglia Guidance Document

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Document uncontrolled when printed

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Background and trial summary

Referral process

Patient immobilisation

Simulation imaging

Treatment planning

Treatment delivery

Delivery quality assurance

# Referral and CIED safety

**Radiotherapy consent form**

The Royal College of Radiologists

This form should only be used if the patient is over 16 years old and has capacity to give consent. If the patient does not legally have capacity please use an appropriate alternative consent form from your hospital.

**Patient details**

Patient name: \_\_\_\_\_ Date of birth: \_\_\_\_\_

Patient unique identifier: \_\_\_\_\_ Name of hospital: \_\_\_\_\_

Responsible consultant oncologist or consultant therapeutic radiographer: \_\_\_\_\_

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**GenesisCare**

**Device information: pacemakers and cardiac implantable electronic devices**

Before a referral can be processed, complete device information should be provided including, manufacturer, model, implantation date for generator and each lead. It is recommended that the responsibility for obtaining this information should lie with the referrer, with support of radiographers and administration staff as required.

Referrer Complete as much information as possible, including department where device was fitted.  
 Radiographers, administration staff Contact department where device was fitted for complete information.

Patient Information			
Title	First name	Surname	
GenesisCare No.	Date of birth		
Department where device fitted			
Date device fitted			
Consultant			
Generator information		Present	Manufacturer
Pacemaker	Yes <input type="checkbox"/> No <input type="checkbox"/>		
ICD	Yes <input type="checkbox"/> No <input type="checkbox"/>		

- Radiotherapy consent plus basic device information provided by Practitioner

**RT-SOP-XXX**

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**GenesisCare**

**MR-Linac Imaging for Individuals with MR Conditional Cardiac Implantable Electronic Devices**

GenesisCare UK

1. Introduction and Purpose

This SOP only applies to patients undergoing MR-Linac imaging (standalone or part of treatment) in specific clinicals trial (detailed below) at GenesisCare Oxford, with support from Oxford University Hospitals NHS Foundation Trust radiology department. Radiotherapy referrals (private or NHS) for treatment of the MR-Linac for patients with CIEDs are not currently accepted.

The unique imaging characteristics of MRI make it an increasingly vital modality in many diagnostic and treatment pathways. Simultaneously, implementation of cardiac implantable electronic devices (CIEDs) are rising and there are currently half a million people in the UK with either of the two classes of device in category: cardiac pacemakers (PMs) and implantable cardioverter defibrillators (ICDs).

- Detailed device information requested by GenesisCare team

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**GenesisCare**

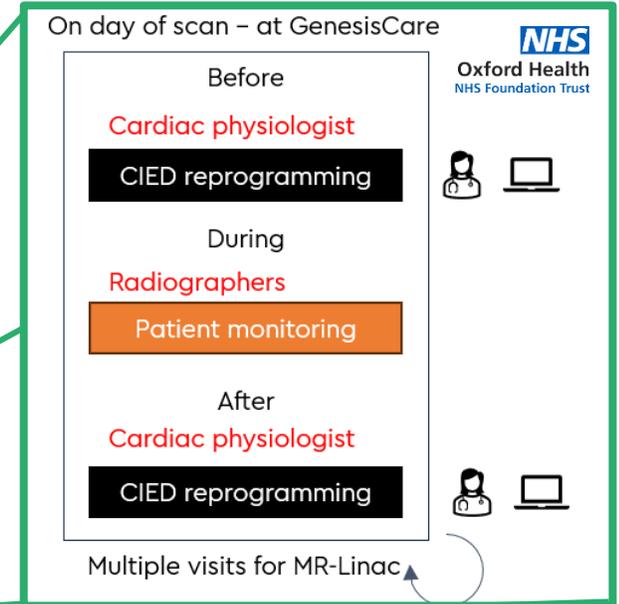
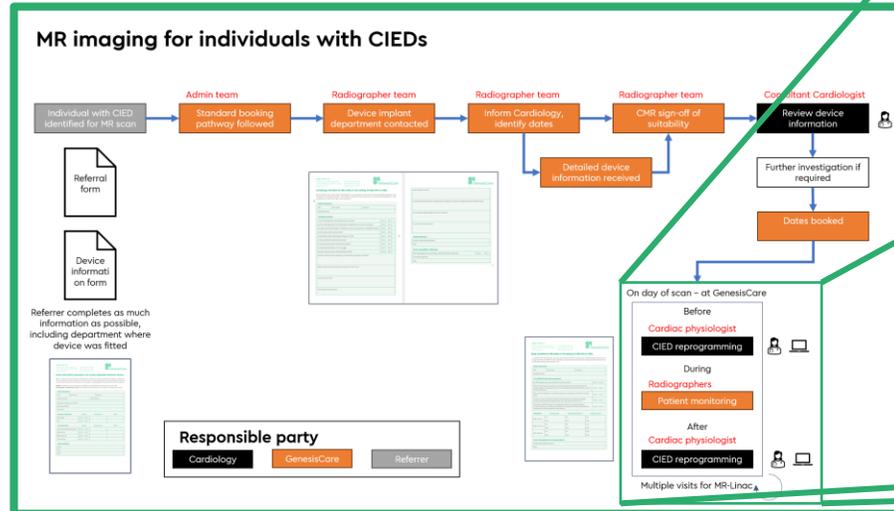
**Cardiology checklist for MRI safety in the setting of CIED (PM or CIED)**

Before the first scan, the Cardiac Physiologist is to interrogate the device during the pre-MRI assessment and complete the following checklist. These device details must be reviewed by a Consultant Radiologist or CMR Consultant to confirm the CIED is MR conditional.

Patient Information		
Title	First name	Surname
GenesisCare No.		
Cardiology checklist		
Correct manufacturer and model details recorded?	Yes <input type="checkbox"/>	No <input type="checkbox"/>
Has the CIED (generator and leads) been implanted for more than six weeks?	Yes <input type="checkbox"/>	No <input type="checkbox"/>
Are there any lead extenders or adapters, fractured, epical or abandoned leads?	Yes <input type="checkbox"/>	No <input type="checkbox"/>
Are the leads electrically intact?	Yes <input type="checkbox"/>	No <input type="checkbox"/>
Is the battery of the CIED approaching end of life?	Yes <input type="checkbox"/>	No <input type="checkbox"/>
Is the pacemaker functionally normally?	Yes <input type="checkbox"/>	No <input type="checkbox"/>
Is the pacemaker sited in the pectoral region?	Yes <input type="checkbox"/>	No <input type="checkbox"/>
Are pacing thresholds <2.0 V at 0.4 ms?	Yes <input type="checkbox"/>	No <input type="checkbox"/>
Pacing mode and site to be set during the MRI?	Yes <input type="checkbox"/>	No <input type="checkbox"/>

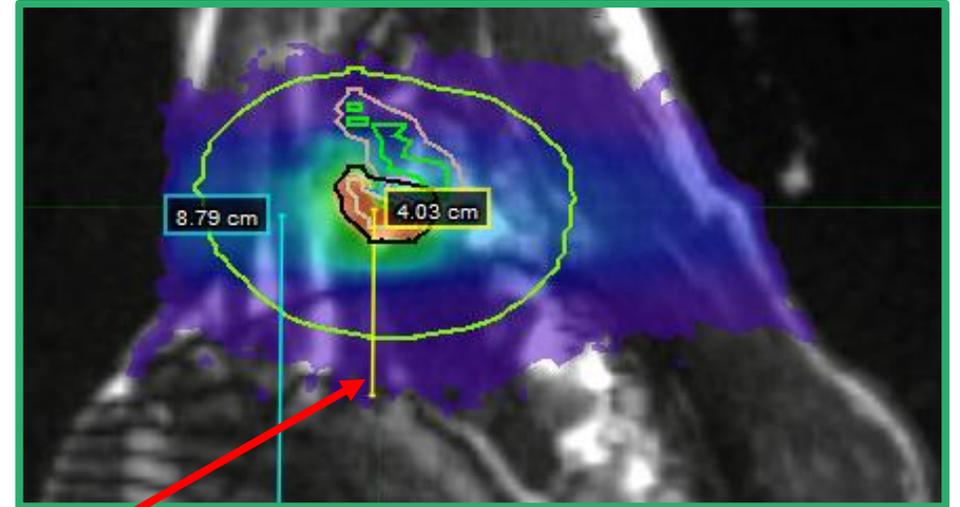
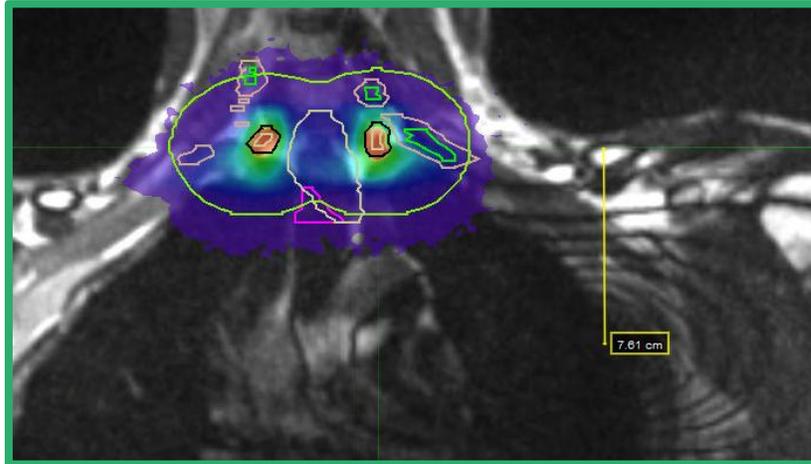
Details of patient status (symptoms, recent illness, episodes, therapies)

- Device safety approved by GenesisCare Consultant Cardiologist
- Practical elements of device reprogramming undertaken by research team



# Estimated doses to CIEDs

Dose to CIED must be kept below 5 Gy



Trial setup allows us to exclude patients where we feel CIED positioning may not allow safe treatment planning.

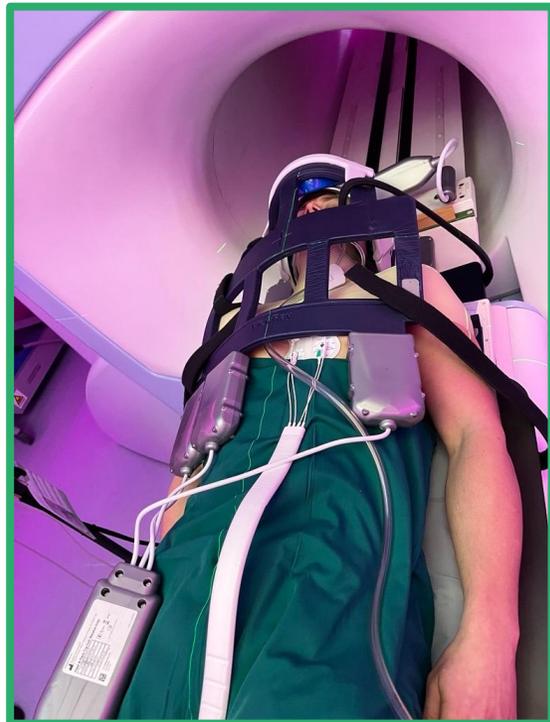
- Safe zone is greater than 4 cm from centre of target region

# Patient immobilisation

- MRIdian head and neck coils
- 5-point open-face masks
- Custom-made support for H&N board



5-point open-face masks



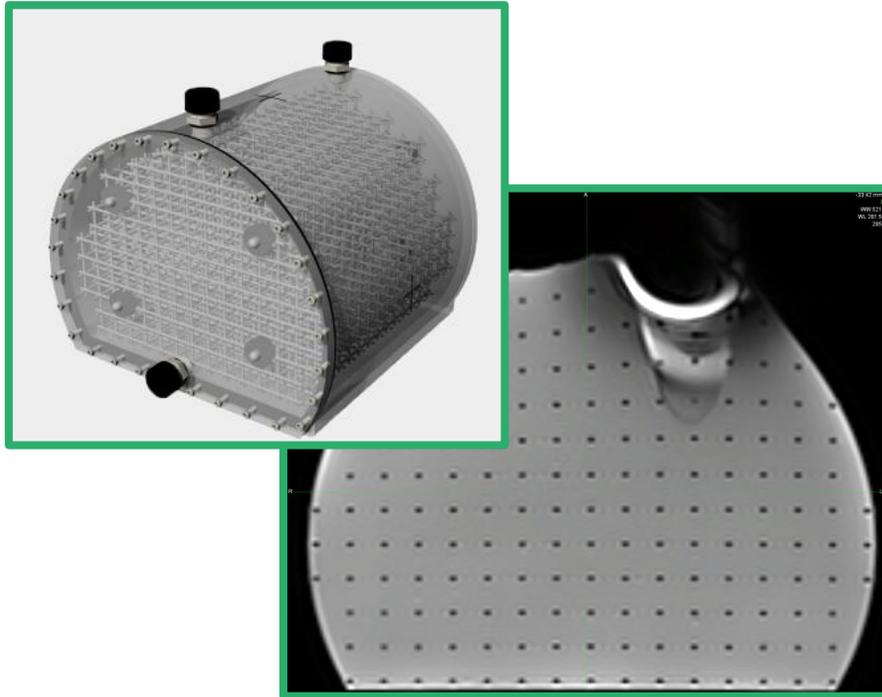
In-house developed MR safe support

# Image distortion in the presence of CIEDs



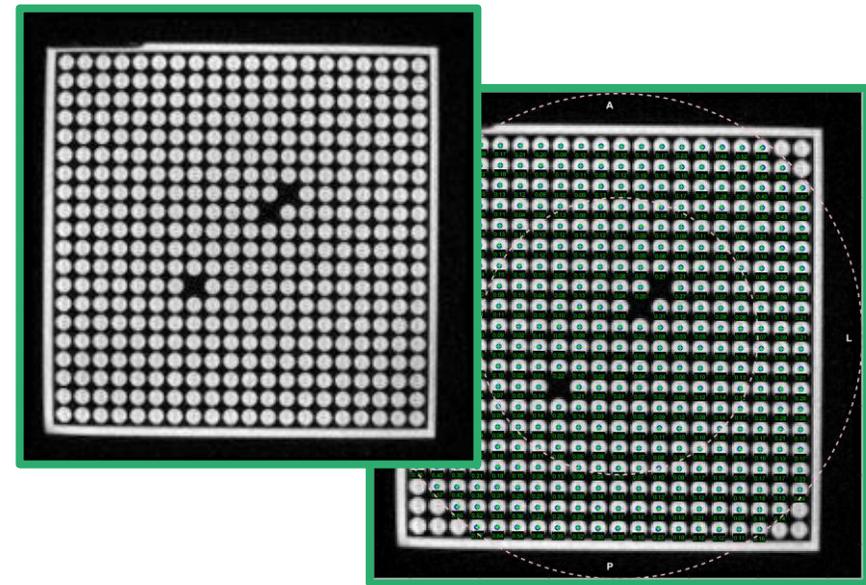
Large Field of View Distortion Phantom

- Acquired on OCMR and MRIdian scanners
- Online analysis software



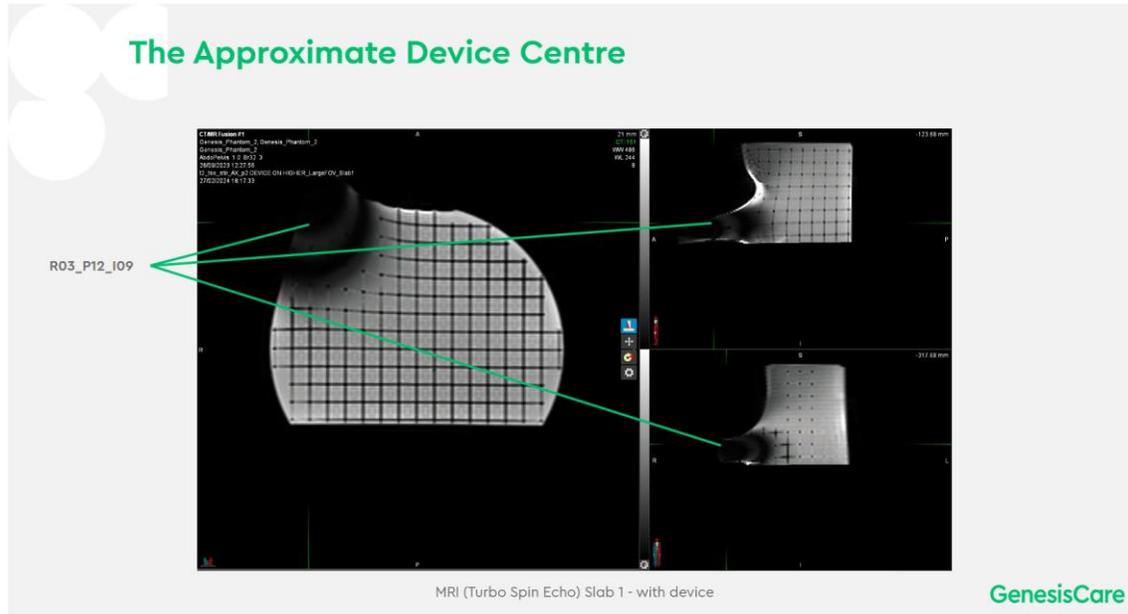
MRIdian 2D distortion phantom  
Part of routine QA programme

- 1 mm within 100 mm radius ✓
- 2 mm within 175 mm radius ✓



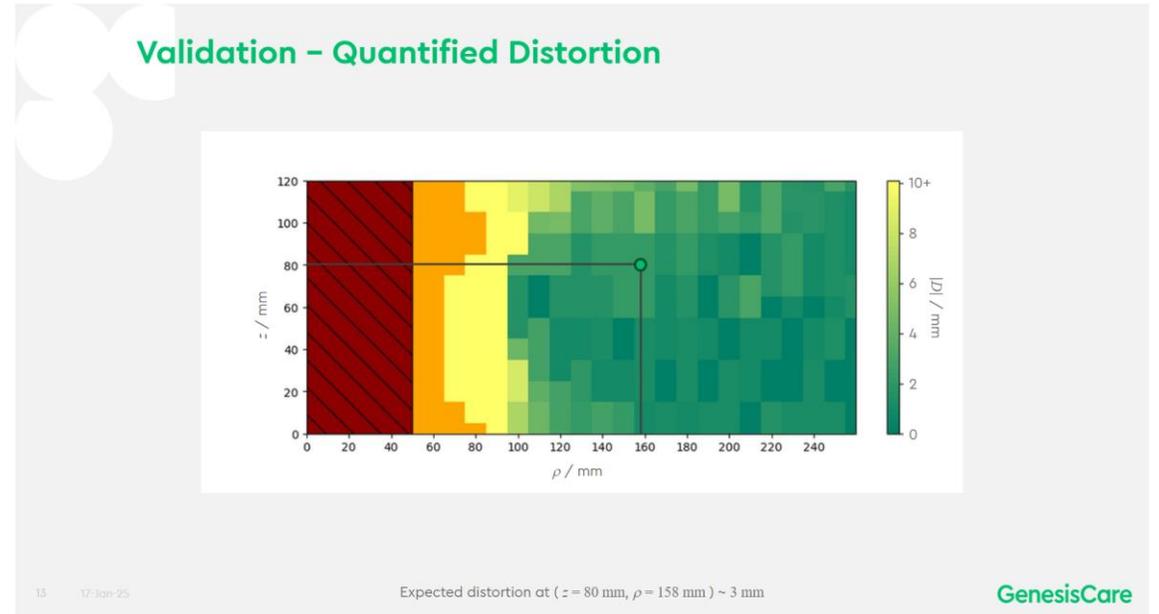
# Image distortion in the presence of CIEDs

## The Approximate Device Centre



CIRS Large FOV phantom on 1.5 T scanner. Significant artefact resulted in the processing software being unable to run correctly.

## Validation - Quantified Distortion



In-house image analysis to assess distortion. Conclusion is that  $>140 \text{ mm}$  from the centre of the artefact, image distortion is not affected.

# Volume definition

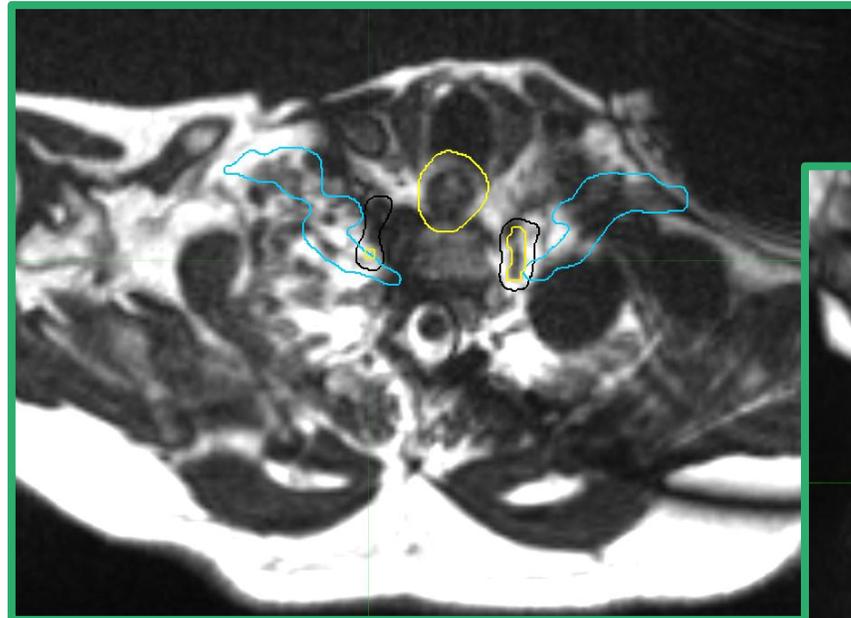
## Treatment target

CTV = sympathetic chain, including lower part of stellate, T1 and T2 ganglia

- PTV\_right = CTV\_right + 3 mm
- PTV\_left = CTV\_left + 3 mm
- PTV\_XX00 = PTV\_right + PTV\_left

## Key organs at risk

- Brachial plexus 
  - Oesophagus 
- 3 mm PRV on both



# Treatment planning

## Dose prescription

- PTV\_XX00: V(100%) = 95%

Cohort	Dose per fraction	Number of fractions	Total dose
1	8 Gy	3	24 Gy / 3#
2	9 Gy	3	27 Gy / 3#
3	10 Gy	3	30 Gy / 3#
4	11 Gy	3	33 Gy / 3#

## Planning aims

- PTV\_R: V(95%)  $\geq$  75%
- PTV\_L: V(95%)  $\geq$  75%
- PTV\_L: 110% < D(0.03 cc)  $\leq$  120%
- PTV\_R: 110% < D(0.03 cc)  $\leq$  120%

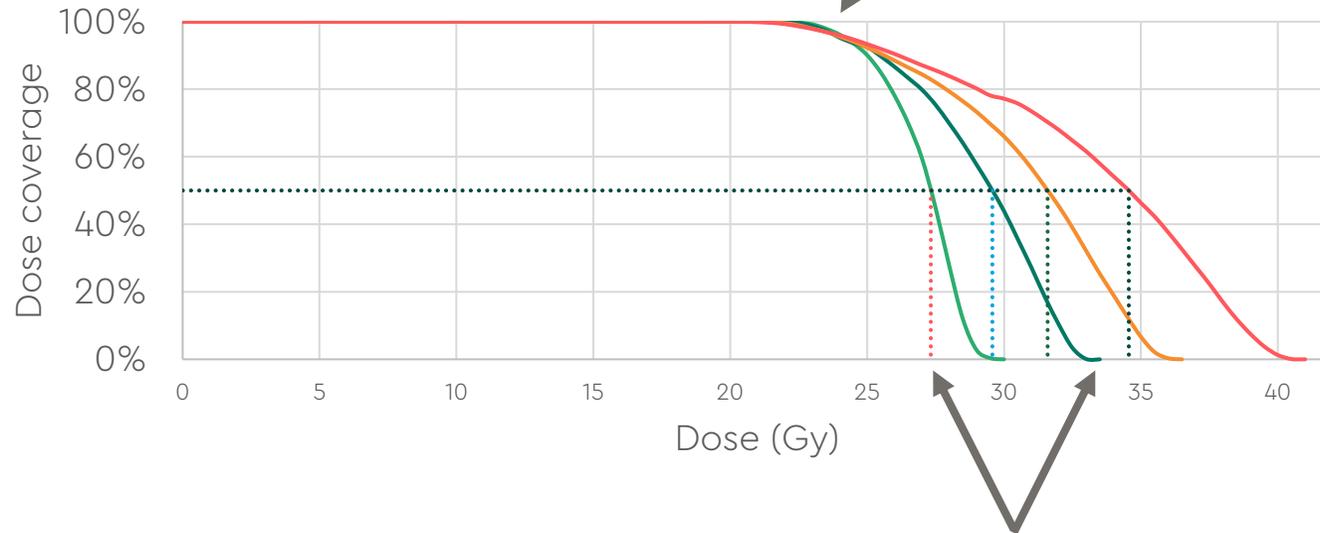
## OAR constraints

Dose limiting structures highlighted

Organ at risk		3 fractions	
Brachial plexus PRV	D(0.1 cc)	$\leq$ 24.0 Gy	Mandatory
Chest wall	D(0.1 cc)	$\leq$ 36.9 Gy	Optimal
	D(30.0 cc)	$\leq$ 30.0 Gy	Optimal
Great vessels	D(0.1 cc)	$\leq$ 45.0 Gy	Mandatory
Oesophagus PRV	D(0.1 cc)	$\leq$ 25.2 Gy	Mandatory
Lungs combined	V(20 Gy)	$\leq$ 10%	Optimal
	V(20 Gy)	$\leq$ 15%	Mandatory
Spinal cord PRV	D(0.1 cc)	$\leq$ 20.3 Gy	Mandatory
Skin	D(0.1 cc)	$\leq$ 33.0 Gy	Optimal
	D(10.0 cc)	$\leq$ 30.0 Gy	Optimal
Trachea	D(0.1 cc)	$\leq$ 30 Gy	Mandatory
Carotid artery	D(0.03 cc)	$\leq$ 32.5 Gy	Mandatory
Thyroid lamina	D(0.03 cc)	$\leq$ 30.0 Gy	Mandatory

# Test planning

Brachial plexus dose constraint limits PTV coverage



Dose level

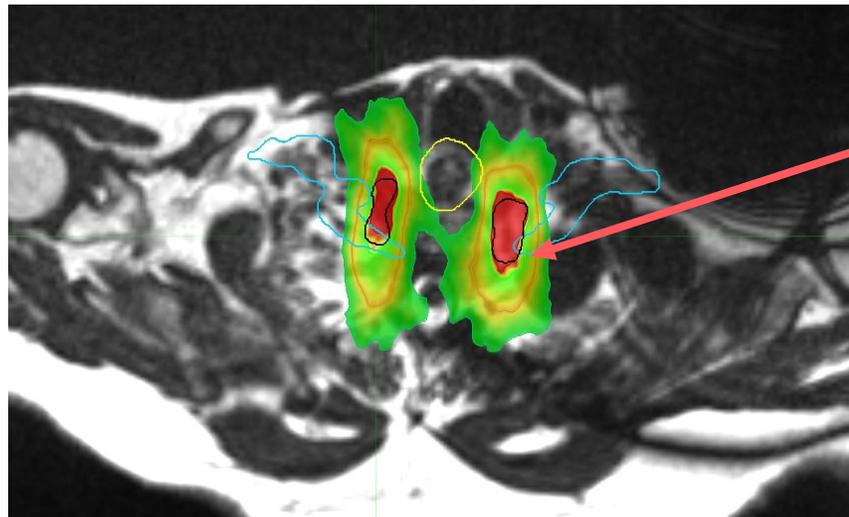
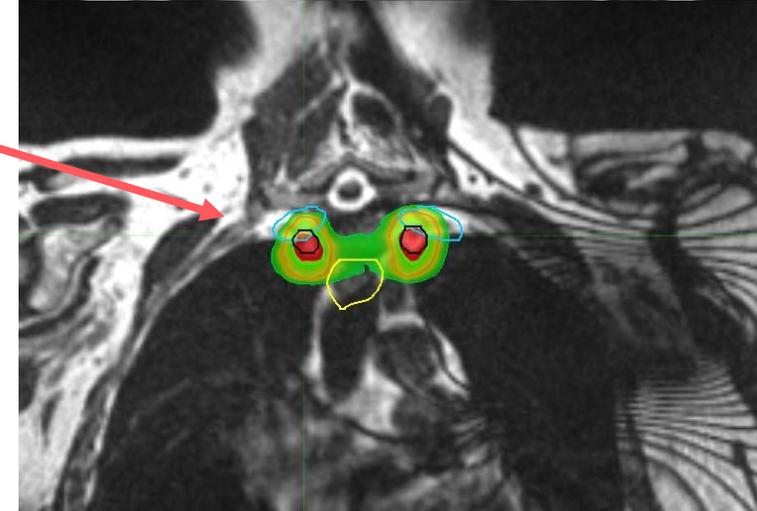
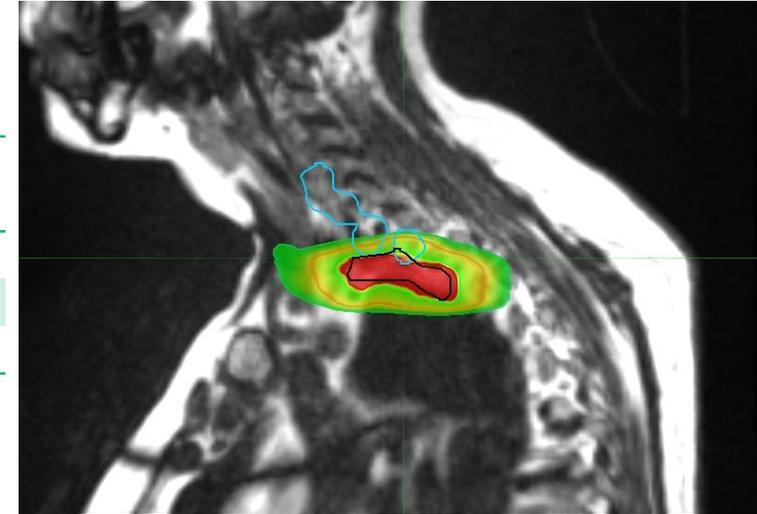
Key metrics

	Minimum	Median	Maximum
	D(98%)	D(50%)	D(2%)
<b>24 Gy / 3</b>	23.5 Gy	27.3 Gy	29.2 Gy
<b>27 Gy / 3</b>	23.3 Gy	29.6 Gy	32.7 Gy
<b>30 Gy / 3</b>	23.0 Gy	31.6 Gy	34.6 Gy
<b>33 Gy / 3</b>	22.9 Gy	34.6 Gy	39.9 Gy

Median and maximum dose increases for each dose level

# Clinical plans

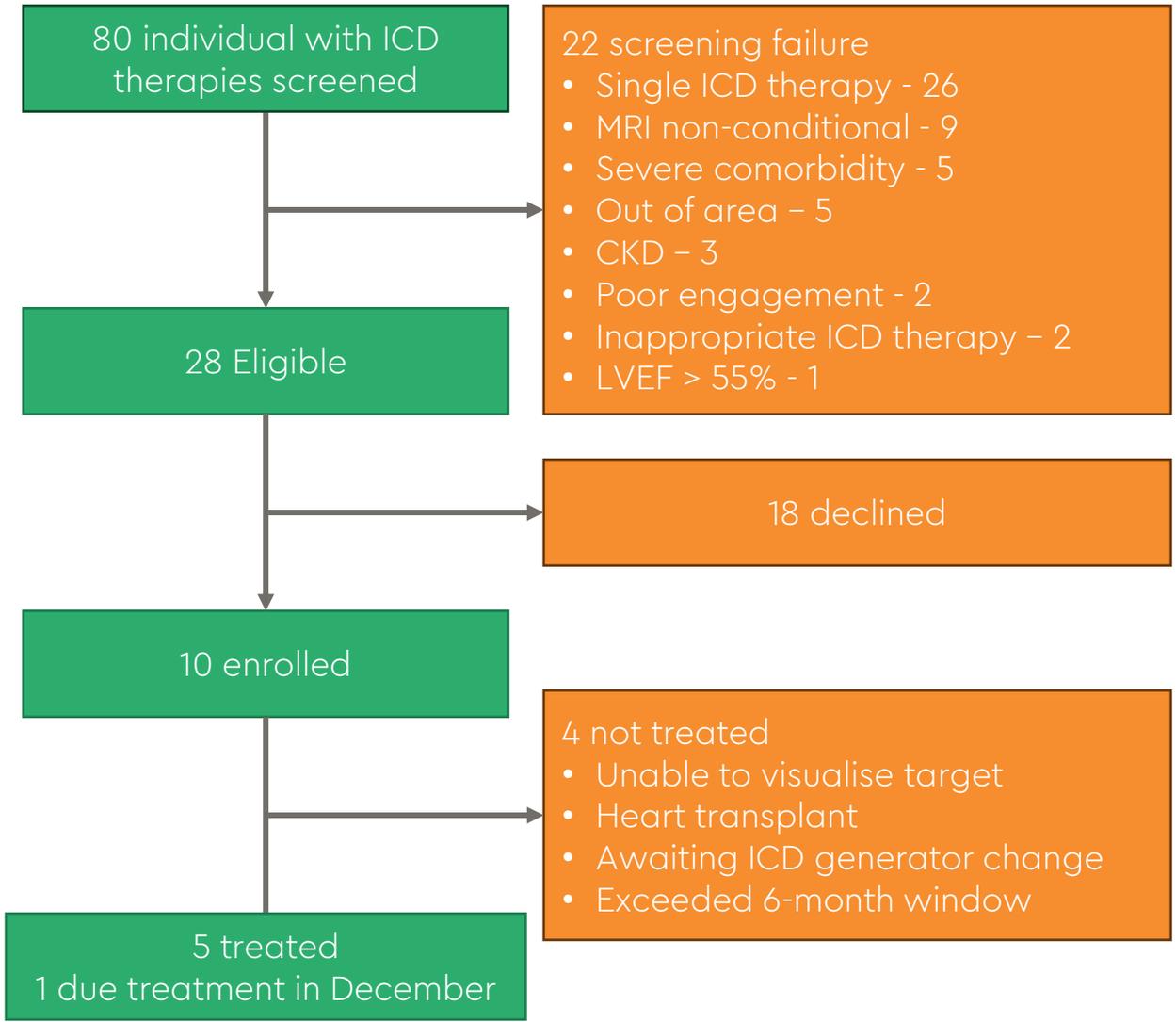
Study ID	PTV volume	PTV		Pacemaker PRV D(0.03 cc)	Brachial plexus D(0.1 cc)	Oesophagus PRV D(0.1 cc)
		V(100%)	D(98%)			
MRAD01	7.4 cc	87.3%	22.3 Gy	4.7 Gy	23.8 Gy	14.8 Gy
MRAD04	9.1 cc	88.4%	22.4 Gy	2.9 Gy	23.8 Gy	16.9 Gy
MRAD08	9.0 cc	86.3%	22.6 Gy	2.0 Gy	23.8 Gy	18.2 Gy



Brachial plexus PRV overlapping PTV, causing compromise of 100% isodose

- PTV\_2400
- Brachial plexus PRV
- Oesophagus
- 24 Gy
- 12 Gy

# Progress so far...

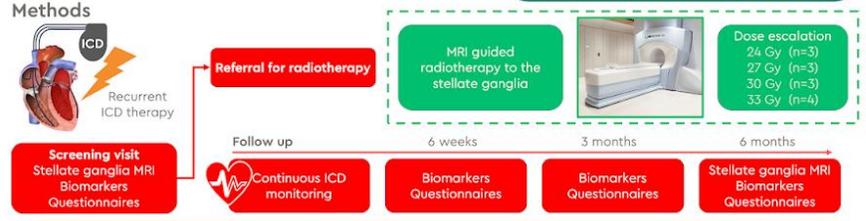


## Hypofractionated Radiotherapy to the stellate ganglia for ventricular arrhythmia (RADIO STAR) trial

Ami Sabharwal<sup>1,2</sup>, Ben George<sup>2</sup>, Ben Bussmann<sup>1,3</sup>, Ebiison Chinerende<sup>2</sup>, Maxwell Robinson<sup>1</sup>, Veni Enzhi<sup>2</sup>, Bleddyn Jones<sup>3</sup>, Fintan Sheerin<sup>1</sup>, Sukumar Prabakar<sup>1</sup>, Tom Whyntie<sup>2</sup>, James T. Grist<sup>3</sup>, Neil Herring<sup>1,3</sup>  
<sup>1</sup> Oxford University Hospitals NHS Foundation Trust  
<sup>2</sup> GenesisCare, UK; <sup>3</sup> University of Oxford

**Background**  
 Heart failure is associated with chronic sympathetic activation which is the trigger for life-threatening ventricular arrhythmias (VA). Implantable cardioverter defibrillators (ICDs) save lives by treating VAs but cannot prevent them from occurring. Recurrent ICD shocks lead to worse outcomes and reduced quality of life. Cardiac sympathetic denervation by surgical removal of the stellate ganglia has been shown to be highly successful in preventing VA, but suffers from high rates of peri-operative complications<sup>3</sup>.

**Aims/objectives**  
 To assess whether stellate ganglia modification can safely be achieved non-invasively by ultra-hypofractionated image guided radiotherapy. To determine if non-invasive stellate ganglia modification has a favourable safety profile compared to surgical denervation. To evaluate if non-invasive stellate ganglia modification leads to a reduction in ICD therapies and improved quality of life.



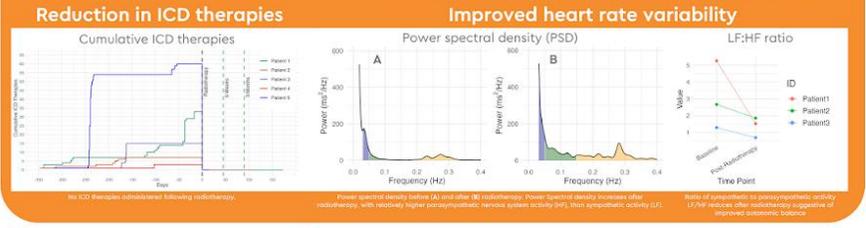
**Results**

**Planning statistics for cohort 1**

	Patient A	Patient B	Patient C
PTV_L	3.8 cc	5.0 cc	4.3 cc
PTV_R	3.6 cc	4.1 cc	4.8 cc
PTV	7.4 cc	9.1 cc	9.0 cc
PTV_L V(100%)	90.6%	90.8%	86.1%
PTV_R V(100%)	83.6%	85.5%	86.6%
PTV V(100%)	87.3%	88.4%	86.3%
CTV_L D(98%)	25.8 Gy	23.8 Gy	25.0 Gy
CTV_R D(98%)	23.9 Gy	23.6 Gy	23.9 Gy
PTV D(98%)	22.3 Gy	22.4 Gy	22.6 Gy
PPM PRV D(0.03 cc)	4.7 Gy	2.9 Gy	2.0 Gy

**Safety**

- No related SAEs
- No hypotension
- No neurological symptoms
- Mild fatigue



**Conclusion**  
 Radiotherapy to the stellate ganglia is feasible and safe. Early results suggest this is effective at preventing VAs in patient with previously refractory VAs.

**References**

1. Herring N, Kalla M, Provenzon D. The autonomic nervous system and cardiac arrhythmias: current concepts and emerging therapies. *Radiotherapy Cardiovascular Oncology* 2018;10(2):107-18.
2. Probst R, Kottmann GW, Hallsingler AS, Anderson L, Cribben D, Bhatt RK, Reddy RH, MacIntyre JL, Yee B, Guzman V, Tunjajit H. Prognostic importance of defibrillator shocks in patients with heart failure. *New England Journal of Medicine*. 2018;379:1020-9.
3. Shah R, Aoun F, Aljaghibi H, Okada DR, Carabba R, Shivkumar K, Tashir H. Cardiac sympathetic denervation for refractory ventricular arrhythmias in patients with advanced heart disease: A systematic review. *Heart Rhythm*. 2018 Oct;15(10):1479-85.



# Research team

**Chief Investigator** Professor Neil Herring

## Co-investigators (Clinical)

- Ami Sabharwal, Ben Bussman, Finn Sheerin, Veni Ezhil

## Co-investigators (Physics)

- Maxwell Robinson, Ben George, James Grist, Tom Whyntie

## GenesisCare MRIdian team

- Ebison Chinherendre, Joe Drabble

## Radiographers

- Nash Malekhi, Emma Jayne McLean, Emmie Rukoni, Alex Goodman, Roxanne Clelland, Sam Bennett



# Thank you for listening!

