NHS
Health Research Authority

Exploratory study of early biomarkers allowing Dynamic Assessment of Response to Treatment in cancers of the head and neck

Short Title: THE DART STUDY

Protocol version: v1.2

Dated: 19.08.2022

RESEARCH REFERENCE NUMBERS

IRAS Number: 292101

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SPONSORS Number:

FUNDERS Number: ICR/RMH BRC B106 GPCE theme

NIHR | Biomedical Research Centre at The Royal Marsden and the ICR

SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), amended regulations (SI 2006/1928) and any subsequent amendments of the clinical trial regulations, GCP guidelines, the Sponsor's SOPs, and other regulatory requirements as amended.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor

I also confirm that I will make the findings of the study publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

Chief Investigator:

Signature: Date:

19.08.2022

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Name: (please print):

Dr. Ben O'Leary NIHR Academic Clinical Lecturer
The Institute of Cancer Research, London
The Royal Marsden Hospital, London

KEY TRIAL CONTACTS AND PROTOCOL CONTRIBUTORS

Chief Investigator	Name: Dr Ben O'Leary Email: ben.oleary@icr.ac.uk Phone:
Trial Manager/ Trial email	Name: Jeane Guevara Email: jeane.guevara@rmh.nhs.uk Trial Email : dart@rmh.nhs.uk
Sponsor	**The Royal Marsden NHS Foundation Trust** For any enquiries, please contact the trial coordinator listed above or email your enquiry to: gcpcomplianceteam@rmh.nhs.uk
Funder(s)	**ICR/RMH BRC B106 GPCE theme**
Key Protocol Contributors	Name: Dr,Shree Bhide Position: Consultant Clinical Oncologist, The Royal Marsden Email: Shree.Bhide@rmh.nhs.uk
	Name: Professor Kevin Harrington Position: Consultant Clinical Oncologist, The Royal Marsden Hospital, London, Professor of Biological Cancer Therapies, The Institute of Cancer Research, London Email: Kevin.harrington@icr.ac.uk

TRIAL SUMMARY

Trial Title	Exploratory study of early biomarkers allowing **D**ynamic **A**ssessment of **R**esponse to **T**reatment in cancers of the head and neck.
Summarised Trial Design	DART is an exploratory molecular analysis study to assess potential early biomarkers of treatment response in squamous cell carcinoma of the head and neck (HNSCC).
Summarised Eligibility Criteria	• Age 18 years or older. • Patients with histologically confirmed cancer of the head and neck with evidence of recurrent or locally advanced cancer not suitable for treatment with curative intent, or metastatic disease. • Ability to give informed consent for biological sample collection
Planned Sample Size	Up to 50 participants
Follow up duration	Up to 5 years clinical follow up for oncological outcomes
Planned Trial Period	Prospective identification of patients will take place over 4 years.
Objectives	

Primary	Explore circulating tumour DNA dynamics in patients receiving systemic therapies for cancers of the head and neck
Secondary	1. To collect longitudinal biological samples, including blood, saliva, stool and tissue, for molecular profiling, including extraction of DNA for sequencing, RNA for gene expression analysis, expansion of PBMCs, and proteins for proteomic studies. 2. To collect tumour tissue to facilitate molecular analysis of recurrent or metastatic cancers of the head and neck. 3. To isolate live tumour and immune cells for studies of therapy resistance and biology in cancers of the head and neck. 4. Retrieval and analysis of archival primary tissue blocks for comparison with metastatic tumour sites. 5. To correlate assays with clinicopathological data.
Methods	• This is an exploratory molecular analysis study to provide a platform for clinical sample collection and novel biomarker discovery. • Prospective participants will be identified by screening H&N MDT and clinic lists at RMH. • Following informed consent, blood and saliva will be taken at baseline prior to the start of systemic therapy, and then again with each treatment cycle until progression. • Archival samples will be retrieved for longitudinal comparisons. • Patients undergoing biopsy as part of their usual clinical care will have tissue samples taken for research. • Patients may opt in if willing to an additional research biopsy at the outset of treatment and/or at the end of treatment. • Sequencing of tumour tissue will be used to identify genomic aberrations specific to a patient's cancer • These personalised genomic changes will be tracked in the longitudinal plasma and saliva samples. • Clinical outcomes such as progression free and overall survival will be compared for patients with and without a fall in their circulating tumour DNA in the early part of treatment.

FUNDING AND SUPPORT IN KIND

FUNDER(S)	FINANCIAL AND NON FINANCIALSUPPORT GIVEN
ICR/RMH BRC B106 GPCE theme	Sample collection
The National Institute for Health Research	Salary support to Chief Investigator

ROLE OF STUDY SPONSOR AND FUNDER

For this trial some of the duties of the sponsor have been delegated to the Chief Investigator (CI), for example the CI has overall responsibility for the design and development of the protocol. The sponsorship agreement describes the allocation of such responsibilities, and a summary of this can be provided by the sponsor upon request.

ROLES & RESPONSIBILITIES OF TRIAL MANAGEMENT COMMITTEES, GROUPS AND INDIVIDUALS

Name	Ben O'Leary
Role(s)	Chief Investigator
Responsibilities	Including, not limited to: Oversight of project design conduct and reporting Liaison with Research Ethics Committee (REC), and other review bodies, during the application process, and where necessary during, the conduct of the research Ensure adherence to protocol Molecular analysis Analysis and write up

Name	Kevin Harrington
Role(s)	Co-Investigator
Responsibilities	Including, not limited to: Oversight of project design, conduct and reporting Liaison with Research Ethics Committee (REC), and other review bodies, during the application process, and where necessary during, the conduct of the research Ensure adherence to protocol Analysis and write up Emergency Chief Investigator

Name	Shreerang Bhide
Role(s)	Co-Investigator
Responsibilities	Including, not limited to: Oversight of project design, conduct and reporting Liaison with Research Ethics Committee (REC), and other review bodies, during the application process, and where necessary during, the conduct of the research Ensure adherence to protocol Analysis and write up

Name	Jeane Guevara
Role(s)	Trial Manager
Responsibilities	Including, not limited to: Liaison with Research Ethics Committee (REC), and other review bodies, during the application process, and where necessary during, the conduct of the research.

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LIST OF ABBREVIATIONS

AE	Adverse Event
AR	Adverse Reaction
CA	Competent Authority
CI	Chief Investigator
CRF	Case Report Form
CRO	Contract Research Organisation
CTA	Clinical Trial Authorisation
GCP	Good Clinical Practice
ICF	Informed Consent Form
ISF	Investigator Site File
NHS R&D	National Health Service Research & Development
NIMP	Non-Investigational Medicinal Product
PIS	Participant Information Sheet
PP	Per protocol
QA	Quality Assurance
QC	Quality Control
REC	Research Ethics Committee
SDV	Source Data Verification
SOP	Standard Operating Procedure
TMG	Trial Management Group
TMF	Trial Master File

1. RATIONALE AND BACKGROUND INFORMATION

Recurrent head and neck squamous cell carcinoma (HNSCC) has a very poor prognosis, with only half of patients surviving longer than a year after disease recurrence even with optimal treatment [1]. Introduction of PD-1 checkpoint inhibitors, an example of immune-oncology (IO) therapy, has improved outcomes for patients with advanced HNSCC. Some patients demonstrate prolonged responses, though the biology of this is not understood. The evolution of HNSCC on treatment with these agents is unknown and there is an urgent need to address this deficit to drive improved treatment strategies.

PD-1 checkpoint inhibitors have improved the limited survival of patients with advanced HNSCC, with nivolumab approved in the UK for patients pre-treated with platinum chemotherapy[2]. Following results from the KEYNOTE-048 trial of pembrolizumab this drug is currently available in the first-line setting [1]. Available data in other cancers suggests that the factors determining response to IO agents are complex, with a potential role for tumour mutational burden[3], the clonal status of tumour neoantigens [4] with a study in HNSCC highlighting a role for the tumour microenvironment (TME) and immune milieu [5]. A previous longitudinal study in melanoma demonstrated clonal evolution on nivolumab, with evidence of neoantigen-directed immune-editing and changes in the T cell receptor repertoire [6], but there are no longitudinal data available for HNSCC. Due to the complexity of response to IO, dynamic biomarkers have been proposed as an approach that provides a patient-unique in vivo assessment of treatment efficacy [7].

Circulating tumour DNA (ctDNA) can be identified in patients with a wide variety of cancers, and has been shown to allow early prediction of disease relapse after treatment with curative intent in HNSCC [8]. Recent data show that early changes in ctDNA can predict which patients will respond better to systemic therapies[9], including immunotherapies [10, 11] although there are no data for this yet in HNSCC.

The DART Study will begin to address the above deficit through a longitudinal study of HNSCC patients receiving systemic therapy. Dense sample collection will allow a deep translational analysis of tumour evolution and dynamic biomarkers. An initial primary analysis of sub clonal evolution in circulating tumour DNA as an early treatment biomarker is planned, with the study samples also providing a sample collection platform allowing subsequent analyses, such as mapping the genomic landscape of metastatic HNSCC. Tissue biopsies will be collected at the start of systemic therapy with contemporaneous and then longitudinal plasma, and saliva.

2. OBJECTIVES

2.1. Goal

Explore early biomarkers of response to treatment in cancers of the head and neck.

2.2. Primary objective

Explore circulating tumour DNA dynamics in patients receiving systemic therapies for cancers of the head and neck.

2.3. Secondary objectives

1. To collect longitudinal biological samples, including blood, saliva, stool and tissue, for molecular profiling, including extraction of DNA for sequencing, RNA for gene expression analysis, expansion of PBMCSs, and proteins for proteomic studies.
2. To collect tumour tissue to facilitate molecular analysis of recurrent or metastatic cancers of the head and neck.
3. To isolate live tumour cells for organoid and co-culture studies of therapy resistance and biology in cancers of the head and neck.
4. Retrieval and analysis of archival primary tissue blocks for comparison with metastatic tumour sites.
5. To correlate assays with clinicopathological data.

2.4. STUDY SETTING

Participants will be recruited from the Royal Marsden Hospital (RMH), a tertiary referral H&N cancer unit in London, UK.

3. ELIGIBILITY CRITERIA

3.1. Inclusion criteria

I. Age 18 years or older.

II. Patients with histologically confirmed cancer of the head and neck with evidence of recurrent or locally advanced cancer not suitable for treatment with curative intent, or metastatic disease.

III. Receiving immunotherapy

IV. Ability to give informed consent for biological sample collection.

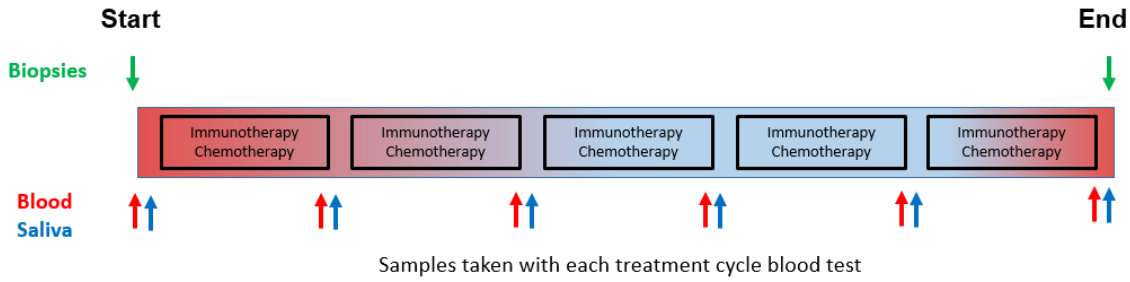
3.2. Exclusion criteria

I. Unable to undergo serial sample collection

II. Pregnancy

4. TRIAL PROCEDURES

	Study entry	Baseline	Treatment	Follow up
Informed Consent	X			
Date of birth		X		
Demographics		X		
Cancer treatment history		X	X	X
Height, Weight & BMI		X	X	
Performance status		X	X	X
Intervention for adverse events		X	X	X
Radiological Tumour assessment data		X	X	X
Blood Sample & Saliva Sample Drawn		X	X	
Next line treatment and survival data				X



Samples taken with each treatment cycle blood test

4.1. Recruitment

Patients undergoing systemic therapy for recurrent, metastatic, or locally advanced cancer of the head and neck not suitable for treatment with curative intent. This is a biological research study involving the collection of blood, tumour tissue, saliva, and other body fluids routinely examined during cancer care (e.g. CSF, ascites, urine, stool or pleural fluids). Routine clinicopathological data including treatment details will be collected in linked-anonymised fashion for correlation and held in a secure database.

Patients consent to serial collection of blood and saliva with every cycle of systemic therapy. In terms of tissue, patients may consent to research biopsies to be taken at the time of routine diagnostic biopsies, or for new research biopsies prior to planned treatment. Patients also consent for access to archival tissue and any future biopsies. At the time of disease progression, the patient may also be asked whether they consent to have an optional new biopsy.

4.2. Patient identification

The DART study team will screen the weekly H&N MDT meetings and clinic lists at the Royal Marsden Hospital (RMH).

4.3. Consent

Prospective participants will be informed of the DART study by a member of their usual care team at RMH during their routine outpatient appointments for follow up of their H&N cancer. Participants will be provided with the Participant Information Sheet and copy of the Informed Consent Form. If they express interest in taking part, then consent will be obtained by a member of the DART team, or an appropriately trained delegate, detailed in the Delegation Log.

Consenting procedures will conform to GCP, local and national regulations. Consent will be for collection of new research tissue cores, establishment of live tumour cell culture, and sequential blood and saliva collection, with additional collection of any excess ascitic, pleural fluid, urine, stool or CSF, in addition to retrieval and analysis of archival and future clinical samples. Stool can be collected at any time convenient to the patient.

The Principal Investigator (or designee) should discuss the study with eligible patients, describing the purpose, research objectives and the schedule of data and clinical sample collection. Patients should be provided with the ethically approved patient information sheet and consent form for review and given sufficient time to consider participation in the study. Written consent should be obtained before any data or clinical samples are collected.

4.4. Withdrawal criteria

Patients may withdraw from the study at any time at their own request, or they may be discontinued at the discretion of the Principal Investigator. This can occur for the following reason:

Patient decision
Lost to follow-up
Pregnancy
Protocol violation
Ineligibility
Patient noncompliance
PI decision

If the patient is withdrawn from the study the primary reason as well as the date of withdrawal will be recorded in the in the Excel Data Tool (combined eCRF and database). Should a patient withdraw consent for their samples to be used in DART their biological samples will be destroyed and tissue samples returned to the site for archiving. Data collected at the point of withdrawal will continue to be used by the study team.

4.5. End of trial

The sponsor will notify REC end of a clinical trial within 90 days of its completion on the last visit of the last patient undergoing the trial.

5. STORAGE AND ANALYSIS OF SAMPLES

5.1. Blood, saliva and other clinical fluid samples

A 30 mL blood sample (3x 10 mL blood collection tube, e.g. Streck or other appropriate) for plasma extraction and collection of buffy coat and/or immune cells will be taken with each treatment cycle and at disease progression. Blood tests will be preferentially taken at the time of venepuncture for routine clinical samples. Patients will also be asked to provide a saliva sample. A stool sample will be collected at some point during treatment convenient for the participant, ideally before commencing.

Blood will be centrifuged to separate plasma and buffy coat, or processed for preservation of immune cells as appropriate, before being labelled and stored at -80^{o}C. Saliva samples will be stored at -80^{o}C. Ascites, pleural, urine, stool or cerebrospinal fluid samples, excess to that required for diagnostic tests, will be collected in a sterile fashion for extraction of cell free DNA and isolation of live tumour cells if appropriate. These samples may be taken at study entry or in the future.

5.2. Tumour samples

This protocol will complement the already established RMH Standard Operating Procedures that are in place for the collection of core biopsies for research purposes in patients with suspicious and/or confirmed carcinoma. If not all sites of disease have progressed following a prior therapy, a disease site that has progressed must be biopsied. A total of 4 research cores should be obtained. The feasibility, appropriateness and safety of additional research biopsies will be made on an individual case basis and in consultation with the involved clinicians.

2X core biopsy (or resection specimen) will be taken with 14G core biopsy needle for formalin fixation and standard paraffin embedding. Sample should be placed in a 20 mL universal container containing 10% neutral buffered formalin and sent for embedding in paraffin to the local Histopathology Department. In consultation with the treating clinicians fine needle aspiration can be considered for lymph nodes where core biopsy is felt to represent an unacceptable risk to safety.

If the patient has standard diagnostic formalin fixed biopsies taken at the same time as research biopsies then NO further research biopsies should be taken for formalin fixation, with all research biopsies taken for fresh tissue as below.

2X core biopsies (or resection specimen) will be taken with 14G core biopsy needle for fresh tissue analysis. Samples should be placed on ice in a 1.5 mL Nunc tube.

If for technical reasons it is not possible for the patient to have 4 cores taken, then a minimum of two cores, one fixed in formalin and one fresh should be taken.

5.3. Storage, labelling and postage of biological samples

All the samples will be collected by appropriately trained staff and labelled in accordance with good clinical practice and local protocols. They will be stored in a way that it is easily accessible. If the patient consents to participate in the study, the name of the study, the study ID and the date of acquisition should also be added to the label. Sample storage will be in compliance with the Human Tissue Act.

The biological samples from each patient will be transferred to the Institute of Cancer Research for further analysis, where samples will be stored in secure facilities. Samples labelled in an anonymised fashion with no identifiable features may be shared with external institutions and collaborators. Biological samples retained for the study will be encoded with a unique identifier and other patient identifiers will be removed prior to storage in order to maintain patient confidentiality.

Laboratory researchers will not have access to any details that identify the patient in almost all circumstances. Certain key individuals within the DART team will be able to link the unique identifier with the patient's identification details. This will allow the collection of clinicopathological data, to complement the molecular assay data resulting from the study.

Patients will be asked to provide written informed consent for access to archived tumour sample excess to clinical requirements, and for extraction of nucleic acids for analysis. Tumour samples may be from the primary cancer, local recurrence, or sites of metastatic disease. Extracted nucleic acids will be stored for future analysis in secure facilities at the Institute of Cancer Research. All samples will be held in compliance with the Human Tissue Act (HTA).

All samples should be sent by post to the following address:

Dr Ben O'Leary
Molecular Oncology
Room 2S8
237 Fulham Road, London SW3 6JB
The Institute of Cancer Research

5.4. Molecular analyses

5.4.1. Nucleic acid extraction

Nucleic acids including DNA and RNA will be extracted from biological samples, with buffy coat used for germline DNA. DNA samples will be subjected to sequencing analysis or other molecular techniques to identify changes relevant to cancer biology and resistance to treatment. The analysis will focus initially on the identification of genomic changes in the tumour which can be identified in the contemporaneous plasma samples as ctDNA at the outset of treatment. The levels of ctDNA will then be followed in a longitudinal manner throughout treatment in plasma and other biological samples. This will allow exploration of whether non-invasive analyses can be used in place of tissue biopsies.

5.4.2. Protein analysis

Biological samples from the study will be analysed by immunohistochemistry, or immunofluorescence, or other techniques for analysis of proteins. Tissue samples may be processed for analysis of proteins using alternative techniques. For patients receiving immunotherapy this will included tumour infiltrating lymphocytes and PD-L1 staining.

5.4.3. Live cell analysis

Fresh tissue sections and other biological samples may be processed in the laboratory to isolate and study live tumour and immune cells. This may include isolation of tumour cells, or stromal and immune cells from the tumour or blood, for in vitro analysis of cellular properties and response to interventions. Live tumour cells or tumour pieces may be introduced into immunocompromised mice in order to study the tumourigenic properties of these cells in vivo and study mechanisms of response and resistance of these cells to drugs in vivo. Immune cells will be separated from blood samples and stored for potential expansion and co-culture.

6. STATISTICS AND DATA ANALYSIS

6.1. Primary endpoint

The level of circulating tumour DNA pre-treatment will be descriptively compared to the levels detected at subsequent time points.

6.2. Secondary and exploratory endpoints

This study will facilitate analyses involving cells within the laboratory. For this standard statistical tests for work of this type will be employed.

6.3. Sample size

This is principally a biological sample collection study aiming to assess feasibility of monitoring early changes in ctDNA. The initial recruitment cohort size of 50 has been chosen to ensure reasonable representation of the most frequently mutated genomic sub groups found in HNSCC. A sample size of 50 allows gives a 75% chance of including at least 4 cases of a genomic sub group with a prevalence of 10% in the HNSCC population (e.g. *CASP8* or *NSD1* mutation), using a binomial model of selection.

For the study of live cells it is anticipated that only a low proportion of samples will grow in culture or in immuno-compromised mice, with approximately 10%-30% of samples generating growth. This is exploratory work and has not been prospectively powered.

6.4. Study duration

The study will continue until up to 50 patients have been recruited and either died or completed 5 years of clinical follow up.

6.5. Planned recruitment rate

No limitation will be placed on the recruitment window.

6.6. Subject population

Patients undergoing systemic therapy for recurrent, metastatic, or locally advanced cancer of the head and neck not suitable for treatment with curative intent. This is a biological research study involving the collection of blood, tumour tissue, saliva, and other body fluids routinely examined during cancer care (e.g. CSF, ascites, urine, stool or pleural fluids). Routine clinicopathological data including treatment details will be collected in linked-anonymised fashion for correlation and held in a secure database.

Patients consent to serial collection of blood and saliva with every cycle of systemic therapy. In terms of tissue, patients may consent to research biopsies to be taken at the time of routine diagnostic biopsies, or for new research biopsies prior to planned treatment. Patients also consent for access to archival tissue and any future biopsies. At the time of disease progression, the patient may also be asked whether they consent to have an optional new biopsy.

6.7. Statistical analysis plan summary

Descriptive statistics only are planned for the primary endpoint.

For the secondary and exploratory endpoints standard statistical tests will be employed. Full details of all analyses will be described in a separate statistical analysis plan.

7. DATA HANDLING

Data collection tools and source document identification

7.1. Clinical data

7.1.1. We will be collecting identifiable data as part of the DART study. This information will be held by the study sponsor on an excel spread sheet stored on a Trust computer in line with local data governance policies and GDPR. Each patient enrolled in the study will have a unique DART Study ID generated**.**

7.1.2. The full dataset is available in an associated Excel Data Tool (combined eCRF and database). The dataset is divided into the following areas:

- General patient details: Demographics, smoking/alcohol and co-morbidities
- Cancer diagnosis: Involved sites, staging, procedures and adjuvant treatment
- Previous treatment: Involved sites, staging, procedures, complications and adjuvant treatment
- Outcome: Survival, recurrence, follow-up

7.2. Source Data

The electronic patient record will form the principal source for clinical data. Data may also be entered directly onto the password protected Excel Data Tool (combined eCRF and database) form where this information would not be collected as part of standard care. As such the Excel Data Tool (combined eCRF and database) may be a source document also.

7.3. Excel Data Tool (combined eCRF and database)

Clinical data will be collected directly onto the password protected Excel Data Tool (combined eCRF and database). This will be stored in the electronic site file on the shared drive for clinical studies conducted by the H&N research team. In accordance with local data governance regulations for patient identifiable data.

7.4. Access to data

Direct access will be granted to authorised representatives from the Sponsor and the regulatory authorities to permit study-related monitoring, audits and inspections, in line with participant consent.

7.5. Molecular Data

Biological specimens will be identified only using the DART Study ID. As such, no patient identifiable data will be processed outside of RMH or by the ICR laboratories.

7.6. Data handling and record keeping

Information related to study participants will remain confidential and be managed in accordance with the Data Protection Act, NHS Caldecott Principles, The UK Policy Framework for Health and Social Care Research', and the conditions of Research Ethics Committee Approval.

All case record forms will be held in the site file, which will be kept in a locked drawer in a locked office at the study site. They will be destroyed after 5 years. All digital data will be stored on a password-protected

NHS computer on site at Royal Marsden Hospital, under the control of the Chief Investigator. Data will be erased securely after 5 years

7.7. Access to Data

Direct access will be granted to authorised representatives from the Sponsor and the regulatory authorities to permit study-related monitoring, audits and inspections, in line with participant consent.

7.8. Archiving

All study documents will be archived by the Royal Marsden Hospital NHS Foundation Trust following submission of the end of study report. Archiving will be conducted in line with local guidelines. These documents will be stored in a location determined by the Sponsor in line with their standard operating procedures. Any destruction of essential documents will require authorisation from the Royal Marsden Hospital NHS Foundation Trust. The minimum requirement for document retention is 5 years.

8 TRIAL OVERSIGHT, MONITORING, INSPECTION AND AUDIT

The Royal Marsden Hospital NHS Foundation Trust is the Sponsor of the study. There are no interventions requiring risk assessment. The following study-related responsibilities have been defined:

- Overall responsibility: Chief Investigator (CI)
- Monitoring study progress: Chief Investigator (CI)
- Operational oversight: Trial Manger
- Data collection: Lead Researchers and Co-investigators
- Consent forms: Lead Researchers and Co-investigators
- Data analysis & interpretation: Chief Investigator (CI)
- Data storage: Chief Investigator (CI) / Data Manager
- Intellectual property: Chief Investigator (CI)

Sponsor and site delegation logs will record which members of staff are appropriately qualified and trained to conduct trial-specific activities.

Trial Management Group

A Trial Management Group (TMG) will be set up and membership will include Chef Investigator, Co-Investigators and Senior Trial Manager. Principal Investigators and other key study personnel will be invited to join the TMG as appropriate. The TMG has operational responsibility for the conduct of the trial. The TMG is responsible for monitoring recruitment, safety and governance of the study as well as collaborating with subsequent translational sub-studies. The TMG will also review any safety concerns and can convene a meeting if significant concerns exist. The TMG will meet regularly (at least 4 times per year) and will send updates to Co-Investigators (via email and/or at Investigator Meetings).

9. ETHICAL CONSIDERATIONS

Ethical approval will be obtained from the Research Ethics Committee (REC) before commencing recruitment and for all trial amendments. All correspondence with the REC will be retained in the Trial Master File/Investigator Site File. The Chief Investigator (or delegate) will produce annual progress reports and notify the REC of the end of the study. If the study is ended prematurely, the Chief Investigator will notify the REC, including the reasons for the premature termination. Within one year after the end of the study, the Chief Investigator will submit a final report with the results, including any publications/abstracts, to the REC. The study

will be conducted in accordance with the conditions of ethical approval. Local R&D Confirmation of Capacity and Capability will be obtained prior to recruitment of patients at collaborating centres.

The protocol will be submitted for ethical review to the Health Research Authority's 'Integrated Research Application System' (IRAS).

The DART Study is sponsored by The Royal Marsden NHS Foundation Trust and will be approved by the Sponsor's Committee for Clinical Research (CCR). The Royal Marsden NHS Foundation Trust will ensure that the study has received ethics approval from a research ethics committee (REC) and has received Health Research Authority (HRA) approval.

10 INDEMNITY

There are no specific compensation arrangements for harmful events which might arise from participation in this trial. However, the study is covered for negligent claims occurring with the NHS by Crown indemnity. There is no pre-existing arrangement for non-negligent claims arising from the conduct of the study.

11 AMENDMENTS

Amendments to the protocol or associated documentation will be made when necessary and should be agreed by the trial management group or equivalent committee. The CI has responsibility for preparing the amendment and deciding whether the amendment is substantial. All amendments will be submitted for sponsorship approval prior to making REC and/or HRA applications and will not be implemented until local R&D confirmation of capacity and capability at the research site has been granted, where appropriate.

Amendments to the protocol will be summarised in the relevant appendix.

12 DISSEMINATION POLICY

12.1 Dissemination policy

Data arising from the study are owned by the Sponsor. Findings will be submitted for publication in relevant H&N or Cancer peer reviewed journals. Funders will be acknowledged in any subsequent reports. Authorship will be granted in line with criteria defined by The International Committee of Medical Journal Editors.

12.2 Authorship eligibility guidelines and any intended use of professional writers

The trial results will be submitted for publication in a relevant medical journal with authorship according to the criteria defined by the ICMJE (http://www.icmje.org). These state that: Authorship credit should be based:

i. On substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND

ii. Drafting the work or revising it critically for important intellectual content; AND

iii. Final approval of the version to be published; AND

iv. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

13 SAFETY REPORTING

All adverse events potentially related a research procedure will be reviewed by two clinicians in accordance with the Royal Marsden's standard operating procedures (RM-CTU/SOP-18). Adverse events will be recorded using the R&D/TEM-21 Non-CTIMP SAE Report Form (other than

Medical Devices). Adverse events should be reported as soon as possible but within a maximum of 14 calendar days.

14 REFERENCES

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15 Appendix 1 – Amendment History

Amendment No.	Protocol version no.	Date issued	Author(s) of changes	Details of changes made
NSA1	1.1	19/08/2022	Orla Batchelor	