# A picture containing text  Description automatically generatedPrecision medicine in laryngeal cancer: development of a laryngeal cancer cohort

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# 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 (and any other relevant) 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 trial publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the trial will be given; and that any discrepancies and serious breaches of GCP from the trial as planned in this protocol will be explained.

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| For and on behalf of the Trial Sponsor: |
| Signature: ...................................................................................................... |  | Date: ....../....../...... |
| Name (please print):...................................................................................................... |  |  |
| Position: ...................................................................................................... |  |  |
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## 1 Background and rationale

Laryngeal cancer affects 2400 new patients each year in the UK. Incidence increases with age and the cancer disproportionately affects those who are socioeconomically disadvantaged. Around half of patients present with advanced disease and, consequently, have poor survival. Those affected are often left with a significantly diminished quality of life: treatment can render the individual permanently nil by mouth due to swallowing problems or in need of a permanent tracheostomy or tracheal stoma. The impact on quality of voice or communication can prevent effective communication. Swallowing difficulty and dry mouth can necessitate permanent gastrostomy tube feeding with effects on socialising and relationships. Laryngeal cancer comprises early (T1 and T2) and advanced (T3 and T4) cancer. Progress in the treatment of both has stalled over the past 30 years. There has been a sea-change in treatment algorithms, with increasing use of transoral laser in early disease and the advent of “laryngeal preservation” in advanced disease. But, over the same time period, survival has remained at best static, and at worst it has declined. From a wider societal perspective, laryngeal cancer diagnosis and treatment costs the NHS £96 million per year with estimated productivity losses of £230,000/patient.

The last reported randomised controlled trial (RCT) which successfully recruited patients and compared surgical and nonsurgical treatments reported in 1991; subsequent RCTs have either compared non-surgical treatments alone or failed to recruit successfully. We have investigated the possibilities of clinical trials in this field, and have recognised the work done to attempt to select patients on the basis of response to up front (induction) chemotherapy. However, induction chemotherapy has repeatedly shown decreased disease control rates. Also, there is no consensus on how tumour response should be measured or defined in RCTs. Moreover, researchers’ and clinicians’ outcome priorities of locoregional control and organ preservations are not necessarily shared by the patient population; indeed, our group has shown that patients will prioritise swallow and voice function over treatment modality or survival. Currently, clinicians have no method of prognosticating how a specific tumour or patient will respond to treatment. For example, one patient with advanced disease treated with radiotherapy will achieve good locoregional control, preserve their larynx, achieve a functional swallow and produce their voice normally. Another patient with the same stage of disease, treated with the same modality, may have persistent disease after 6 weeks of treatment, or will be rendered nil by mouth, gastrostomy fed and dependent on a breathing tube. This has led to clinicians relying on experience and anecdote to guide and support patients though complex decisions. This, in turn, has led to huge variation in treatments delivered across the UK; for example the rate of primary radiotherapy for advanced laryngeal cancer varies across centres from 0% to 83%.

To move forward, we require an understanding of how an individual patient with laryngeal cancer responds to treatment, with respect to both tumour control and functional outcome. Further, clinicians and researchers need to be able to pre-determine this response at presentation. Knowledge of the factors which dictate response to treatment would allow researchers to identify the variables to control for when designing future RCTs of novel treatments. However, risk prediction or precision medicine in laryngeal cancer remains elusive. Clinical cohorts, enriched with rich clinical data and biological samples, are an invaluable resource for advancing precision medicine. In head and neck cancer, audits and previous cohort studies have examined, to some extent, processes of care and survival. This has allowed some initial hypothesis generation; however ambitions to include patients with all cancers have limited the usefulness of the data and clinical engagement. The largest such cohort, the “Head and Neck 5000 study” (HN5000), collected longitudinal data on 5000 patients (1065 with laryngeal cancer) with 3 year survival and patient reported outcomes, but clinical data and samples are limited. However, the endeavour does establish proof of concept and a blueprint for a specific laryngeal cancer cohort.

In other cancers sites (breast, prostate, lymphoma), biochemical analysis of biopsy samples allows the tailoring of specific treatments to an individual tumour; unfortunately in laryngeal cancer researchers have not made such progress. This is partly due to the heterogeneous tumour biology of carcinogen-induced malignancies and partly because this cancer attracts little research interest and spending (0.8% of cancer research spend in 2018/19 ). There are potential prognostic markers under investigation: either patient-based (tobacco use, muscle mass) or tumour-driven (the immune checkpoint inhibitor complex IDO, ‘immunoscore’, PDL-1). Although the latter are under investigation for response to novel chemotherapeutic agents, their presence does not currently influence the choice of primary treatment. The emerging field of “radiomics” uses the raw data from routine CT scans and maps this to tumour and patient outcomes as a “radiological biomarker”. This means that although every patient with laryngeal cancer undergoes tissue biopsy and cross-sectional imaging, much of the data goes to waste.

A cohort study of all laryngeal cancers, enriched with samples and detailed clinical data, would be a major step towards defining precision medicine in laryngeal cancer and, in the longer term, to improving patient outcomes. It would allow significant progress in areas including: comparative (treatment) effectiveness research; investigation of biochemical and radiological biomarkers (mapped to treatment outcome); mapping clinical and patient characteristics to outcome; patient involvement in decision making; and the identification of variables for further investigation in trials of novel prognosticators or therapeutics.

## 2. Research questions

1. How do survival and quality of life outcomes compare between surgery and (chemo)radiotherapy in early and advanced laryngeal cancer?
2. How do the presenting features of laryngeal cancer influence oncological, functional and quality of life outcome?

## 3. Primary objectives

1. To assess the difference in disease specific and overall survival between treatment modalities in early and advanced laryngeal cancer
2. To assess the impact of laryngeal function, patient-derived clinical features and tumour factors on treatment outcome in early and advanced laryngeal cancer and use this to develop a risk prediction tool
3. To establish a disease database of 150 laryngeal cancer patients including demographic details, quality of life and laryngeal function
4. To assess the difference in quality of life, swallow and voice outcomes between treatment modalities in early and advanced laryngeal cancer
5. To develop the pathway for routine tissue and radiological scan collection for future studies, mapped to outcome

### Secondary objectives

1. To establish consent processes to allow researchers to re-contact patients for data on long term outcome and survivorship
2. Using the data, establish an initial risk communication tool in the disease

## 4 Trial design

This study is the first enhanced laryngeal cancer disease cohort. We aim to deliver a cross-sectional study of a minimum of 150 patients recruited over a 3-year period

This study will be pragmatic, involving patients with laryngeal cancer attending hospital as part of their routine care. Patients will be identified by a member of the research team and recruitment will be supported by the research team.

## 5 Trial Procedures

### 5.1Recruitment

* Eligibility criteria
	+ Confirmed new diagnosis of laryngeal cancer (Group 2)
	+ Suspected but unconfirmed laryngeal cancer (Group 1)
	+ Age over 18
	+ Capacity to consent
	+ Ability to understand written and spoken English
* Exclusion criteria
	+ Age under 18
	+ No capacity to consent
	+ Recurrence or second head and neck primary cancer
	+ Not able to adequate understand written on spoken English

### Group one: likely laryngeal cancer

Patients with a likely diagnosis of laryngeal cancer will be identified by the clinical team at the time that laryngeal cancer is suspected. The patient is given the participant information sheet (PIS) by the clinical team at the time of the clinic appointment or is sent a copy of the PIS by a research nurse after the clinic appointment has taken place. On the day of the biopsy, they are then approached by a member of the research team and given an opportunity to ask any questions about the study. Patients’ eligibility to the study will be confirmed by a member of the research team, and if eligible, informed consent will be gained. Specific consent will be gained to inform the participant’s General Practitioner (GP) regarding participation in the study. If the biopsy does not confirm cancer, the patient will be withdrawn from the study and any data collected so far will be destroyed. Patients with a biopsy confirming laryngeal cancer will be eligible to continue in the trial and move to Group 2.

### Group two: confirmed laryngeal cancer

Patients who have laryngeal cancer confirmed by biopsy who have not been enrolled into the study previously will be identified by clinical staff at the clinic following their diagnosis of laryngeal cancer by biopsy. At the time of diagnosis, they will be given the PIS, consent form and the preliminary questionnaires.

At the time of the clinic appointment where laryngeal cancer has been confirmed, the pathway of the two patient groups will be the same.

Patients consented into the study will be asked to fill complete a range of questionnaires about their quality of life and laryngeal function (see “baseline data”).

The patient details, demographic and clinical information (together with the data above) will be recorded into the REDCap database by a member of the research team.

This study will not, in any way, affect usual patient care.

The patient is free to refuse participation without giving reasons and without this affecting the care they receive. The participant is free to withdraw at any time from the trial without giving reasons and without prejudicing their further treatment. Participants are provided with a contact point where they may obtain further information about the trial in the PIS. Data and samples collected up to the point of withdrawal will be kept. A person is assumed to have the mental capacity to make a decision unless it is shown to be absent.

All patients who are identified before their biopsy, have a cancer recurrence or who have a resection will be eligible for consent for storage of their tissue. This consent details that their tissue will be stored indefinitely and can be used for future, as yet undecided studies. All potential future studies will have separate ethical approval. Patients have the option to give consent for further biopsies (often in the case of recurrence) to be collected and transferred to a biobank I.e. to be collected and stored for use in future research projects. All patients also consent to being contacted in the future about further research studies and their details being stored for this reason. In all cases, tissue which is stored under each establishment Human Tissue Authority (HTA) licence

5.2 Baseline data

The following data are collected on all patients, additional study questionnaires will be collected at any time before the patient begins treatment for their laryngeal cancer.

* Clinical data
	+ Age
	+ Date of birth
	+ Gender at birth
	+ NHS number
	+ Hospital/Trust of treatment
	+ GP Postcode
	+ Date of biopsy
	+ Date of initiation of treatment
	+ Aim of treatment
	+ TNM stage
	+ Smoking history
	+ Alcohol history
	+ ACE score
	+ Clinical frailty scale (CFS)
	+ WHO performance status
	+ Weight
	+ Presence of tube feeding
	+ Treatment received (see later)
* Radiological data
	+ Laryngeal subsite(s) affected by tumour: eg supra / infra hyoid epiglottis, AE fold, false cord, ventricle, true cord, subglottis, AC, paraglottic space, arytenoid, cricoarytenoid joint, cricoid
	+ Cartilagenous framework involvement (inner cortex, extralaryngeal spread, invasion into strapsgross, into straps etc)
	+ Tumour maximum dimension
	+ Extralaryngeal spread
	+ Bilateral involvement
	+ Tumour maximum SUV (if PET scan has been performed as part of routine care)
	+ Signs of aspiration
	+ Cervical lymph node involvement
		- Evidence of extra-capsular spread
* Functional and quality of life data
	+ EORTCQLQ-C30
	+ EORTC HN35
	+ Vocal cord function
	+ FEES/VFSS
	+ DIGEST VFSS/FEES scale
	+ PSS-HN
	+ MDADI
	+ VHI-10
	+ Water swallow test
	+ Minimum phonation time
	+ GRBAS scale
	+ Normalcy of diet subscale
	+ Understandability of speech
* Histological information
	+ From biopsy
		- Histology
		- Grade and differentiation
		- Digital photography if available
	+ From resection
		- Digital photography if available
		- Primary site
		- Dimension
		- Primary site
		- Uni/multifocal
		- Histology
		- Differentiation
		- Invasiveness (mucosa, paraglottic space, pre-epiglottic space, cartilage invasion, extra-laryngeal spread)
		- Invasive front
		- Perineural invasion
		- Lymphovascular invasion
		- Closest margin
		- Pathological TNM staging
		- Neck disease
			* Total number of nodes dissected
			* Total number of involved nodes
			* Perinodal fibrosis
			* Extra-capsular spread
			* Levels of involved nodes
			* Laterality of involved nodes
* Voice recording
* Treatment received
	+ Primary non-surgical treatment
		- Chemotherapy
			* Agent
			* Doses delivered
		- Radiotherapy
			* Dose
			* Fractionation
	+ Primary surgical management
		- Procedure performed
		- Post-operative chemotherapy agent and dose
		- Post-operative radiotherapy dose and fractionation
* Date of completion of treatment

### 5.3 Trial assessments

There will be trial data collection points at 6, 12 and 24 months. At each of these time points, the following data will be collected. Due to variation in routine patient follow up, study data will be collected at visits ± 2 months for the 6 month and 12 visits, and ±3 months for the 24 month visit.

* Clinical data
	+ Disease status
		- Alive without disease
		- Alive with disease
		- Death (disease related)
		- Death (non-disease related)
	+ Smoking history
	+ Alcohol history
	+ ACE score
	+ Weight
	+ Presence of tube feeding
* Functional and quality of life data
	+ EORTCQLQ-C30
	+ HandN35
	+ Vocal cord function
	+ FEES/VFSS
	+ DIGEST VFSS/FEES scale
	+ PSS-HN
	+ MDADI
	+ VHI-10
	+ Water swallow test
	+ Minimum phonation time
	+ GRBAS scale
	+ Normalcy of diet subscale
	+ Understandability of speech

### 5.4 Ad-hoc follow-up assessments

If a patient has a scan as part of their routine care, the scan will be stored and the radiological data will be reported and collected as above

If a patient has a cancer recurrence, as well as the radiological data outlined above, the tissue will be collected and biobanked as discussed in the consent section above. In the event of a recurrence, the data collected will be the same as a primary disease presentation

Patients will be followed up until 24 months (+/- 3 months) years after the completion of their last treatment. As far as possible, research visits will be timed with clinical visits in accordance with visit window schedules.

Patients will be enrolled in the study until their final visit or date of death, if occurs within study period.

Patients from Group 1 who are ineligible for inclusion into Group 2 will be withdrawn from the study and subjects replaced. Patients who withdraw from the study during the enrolment period will be replaced. Withdrawn subjects will be replaced until at least 150 eligible patients have completed the study endpoints.

### 5.5 Adverse Events

As this is an observational study, there are no expected additional adverse events specifically associated with the study. If serious adverse events (SAE) or significant unexpected serious adverse events (SUSAR)’s occur in patients at the time of recruitment to the study within recruiting centres these will be managed locally according to local organisational protocol.

### 5.6 Storage and analysis of clinical samples

#### Types of samples and data to be collected

Tumour tissue- biopsies at diagnosis, during treatment or on relapse or tissue obtained at surgical resection- at presentation, during treatment or on relapse

#### Organising sample retrieval

The procedure for sample retrieval will depend on the nature of the sample requested. Fresh tissuemay be needed for rapid freezing- typically in liquid nitrogen prior to transfer in a frozen state or for disaggregation prior to transport in specialised medium. The preparation and transfer of these samples will require input from an on-site pathologist who will need to decide which samples can be set aside for research once tissue needed for routine clinical care has been removed. Input may also be required from a technician who will follow the relevant protocol for handling samples prior to transport- for example rapid freezing, sample disaggregation and placing samples in the appropriate transport medium. All the necessary materials needed for sample preparation will need to be provided to the hospital.

#### Sample processing

Sample processing will be performed in the local pathology laboratory. Services offered include

a) Sectioning and staining of sections

c) Digital imaging (copies of digital images may be retained in the LARCH database)

d) Immunohistochemistry and optimisation of immunohistochemical techniques

e) Estimates of tumour infiltration

f) DNA extraction from slides- with and without laser capture microdissection

g) Tissue microarrays

On completion of processing samples will be pseudonymised and transferred to clients or the biobank using specialist courier services (PDQ). All material will be stored under each establishment Human Tissue Authority (HTA) licence

#### Withdrawal of consent for tissue storage

If consent is withdrawn for issued samples by the donor, recipients will be informed of the relevant sample numbers and asked to return any unused samples. Results obtained from samples that have already been used for research need not be destroyed.

### 5.7 Routine imaging and radiomic analysis

All scans taken as part of routine care will be stored on hospital servers (as is usual practice). If not already in Newcastle, many of these scans will be transferred using the routine PACS transfer service, to Newcastle. These scans will be subjected to radiomic analysis: scans will be extracted in DICOM format anonymised ensuring removal of all patient identifiable information. Subsequently images will be analysed using LifeX. Images will be allocated with a random number and radiomics analysis will be blinded. Subsequently an array of textural features will be extracted from the images such as conventional indices, first order features, Grey-level Zone Length Matrix, Grey-Level Run Length Matrix, Neighborhood Grey-Level Different Matrix, Grey Level Co-occurrence Matrix. Validated harmonisation techniques will be used to account for multi-centre scanner variability

## 6 Statistics and data analysis

Patient data and information will be collected, stored and used based upon patient consent, and consistent with GDPR requirements. Descriptive statistics will be used to describe the recruited cohort and data completion (at baseline and at follow-up). Baseline characteristics will be compared with routine data (from Hospital Episode Statistics) to determine whether the recruited sample is representative of laryngeal cancer patients across NHS in England.

Depending on the maturity of the cohort at the conclusion of the study, data will be used to start to develop risk prediction models and compare outcomes by treatment modality. Multiple logistic regression analyses will be used to (i) identify patient-related, clinical and health service-related (e.g. institution) factors associated with receipt of surgical vs non-surgical treatment; (ii) quantify locoregional control and identify factors associated with control overall and by treatment modality; and (iii) identify factors associated with quality-of-life overall and by treatment modality. Epidemiological approaches to support treatment comparisons within observational datasets (e.g. propensity scores, instrumental variable analysis) will be used. These analyses will provide an early demonstration of the value and potential of this new cohort.

The planned analyses will draw on a range of epidemiological analytical approaches. They will explore utility of high dimensional propensity scores (which incorporate additional variables in the propensity score, such as clinician and/or hospital characteristics, with these serving as proxies for unmeasured confounders) and instrumental variable analysis (which relies on the existence of an ‘instrument’, a variable that is related to the treatment but not to the study outcome other than through treatment effects).

## 7. Regulatory Issues

### 7.1 Ethics approval

The study will be conducted in accordance with the recommendations for physicians involved in research on human subjects adopted by the 18th World Medical Assembly, Helsinki 1964 and later revisions. The majority of the interventions delivered take place as part of routine care, with LARCH providing a mechanism for recording this data. Ethical approval for the project will be sought from an NHS REC

### 7.2 Consent

Potential participants will be assessed by a member of the study team, eligibility will be confirmed and baseline assessments performed. Consent to enter the study will be sought from each participant only after a full explanation has been given and the PIS has been given

Consent to additional elements of the research will be driven by patients’ wishes giving them control over how their data is used. Patients will be offered the opportunity to consent to the following:

* Consent for future contact with information about studies that become available
* Consent for future contact for collection of additional information regarding this study
* Use of anonymised information or samples collected from this study to be used in future studies which have received separate ethical approval

Patients may consent to as many or few parts as they wish.

### 7.3 Confidentiality and data management

The Caldicott Principles and General Data Protection Regulation (GDPR) will be fully adhered to when dealing with patient identifiable data.

Within each recruiting site the Principal Investigator will preserve the confidentiality of participants taking part in the study. Within sites no staff beyond the usual care team and local research team will have access to identifiable data. The data will be held at the site in accordance with local Trust policies and will be destroyed following the study close in accordance with local Research and Development protocols.

The study team will have access to the full dataset but other users will be restricted to data from their own centre. Access will be via secure portal. Local sites will have access to their site data. The legal basis on which patient data will be held is public interest/scientific research. Consistent with the GDPR principles of fairness and transparency, the study information materials will clearly state what data will be held, where it will be held, what will be done with it, and who will have access to it. The data controller will be provided with these details. We will work with our PPI representatives to ensure that these materials are concise, clear and easy to understand. As noted above, the consent form will be designed so that participants need not opt into all aspects of the study; instead they will be able to opt out of those which they do not wish to be involved in, giving them control over how their data is used.

A purpose-built database and web portal will be developed to support the capture of patient recruitment and study participation data. Only authorised individuals will have login credentials to input this data. The staff (including research nurses within recruiting centres) will be able to remote access the portal to transfer the data. Staff will be a delegated out by Principal investigator based on skills, training and experience; these will be used to restrict access to confidential or otherwise sensitive data. Our web portal will be deployed using REDCap is a browser-based Electronic Case Report Form (eCRF), suitable for Newcastle-led non-commercial research studies. This system site on HSCN (ie the data is securely behind the NHS firewall).

File sharing within the project will be over the Newcastle University OneDrive infrastructure via a Shared Folder that only project members will have access to. All non-digital documents will be stored in locked cabinets in secure offices or areas which require swipe card access at their local sites of recruitment. Where possible, for these documents, patient identifying details will be stored separately from data.

All data collected will be clearly labelled to ensure that file content can be identified. All digital data will be stored in the OneDrive shared project folder or entered into the purpose-build research data web portal as described above. Names used for files will reflect the data that are contained within the files. Dates will be included in files to allow cross-referencing back to written research records. The web portal will maintain access logs for all data entry and queries (logs will include the date, time and user id). Data generated by the research project will be retained after publications resulting from the research are finalised. Data will be stored for 20years. After 20 years data will be considered for longer-term retention based on the published results and further advances in the field of research internationally. Datasets stored for >20 years will be anonymised.

Patient-identifiable data will be held within the database and the main risk is unauthorized or inappropriate access leading to a breach in data protection. The data will be obfuscated depending on who is accessing it and for what purpose. Data Managers, and anyone else who has a legitimate reason for accessing patient-identifiable data will be able to do so; other users will be restricted to pseudo-anonymised data. In the longer-term, for researchers undertaking approved studies using the data, access to identifiable data (e.g.in order to contact patients about participation in a new research study) will be on the basis of agreement from the Study Management Group (SMG), ethical approval & patient consent.

At the end of the study, strategies to promote and publicise the cohort and processes for gaining access to data, samples and/or the recruitment network will be developed and widely publicized and promoted. These will include: information on the cohort website; designated contact point for further information and/or support; flyers, stalls or sessions at scientific and stakeholder conferences; webinars and/or podcasts, and providing a DOI created through data ncl (https://data.ncl.ac.uk/) for inclusion on the project website and published papers.

The data sharing policy, and the procedures (including application forms) for requesting access to the cohort, will be made available on the cohort website. Currently it is anticipated that applications will be prioritised based on: quality; alignment with our vision; potential to translate into clinical practice and/or deliver significant patient/public benefit; collaborative approach; and added value. The cohort research committee will have responsibility for reviewing and approving/declining requests for access.

Data held in the cohort database will be offered for sharing once: (i) the principles on which applications will be reviewed, prioritised and approved are agreed within the collaboration; (ii) the processes for applying to access the cohort are agreed and implemented; (iii) reasonable numbers of patients have been recruited to the cohort. Investigators of adopted research studies will develop their own timelines for data sharing. A requirement of cohort approval will be that data are made available for sharing at as early a point as possible. For these studies, we currently anticipate that the applicant, research partner and other partners and collaborators will have access to the data for 1-2 years after the end of data collection for the study. Patients recruited to the cohort will be asked for consent to data sharing. For the cohort adopted studies, it will be a requirement of adoption that consent is obtained from recruits for data sharing. The major delay to data sharing which will occur relates to the need to establish procedures for study review and adoption

The SMG will make the decision on data access. Committee membership will include the chief investigator (DWH) and co-investigators (JOH and LS) and PPI representation. This group will act as gatekeepers for the data. Decisions on whether or not an application is approved will be recorded together with, in the event the application is declined, reasons and whether the applicants may re-apply if they fulfil certain conditions.

The Newcastle upon Tyne Hospitals NHS Foundation Trust, as data controller, will require data sharing agreements with all organisations responsible for submitting and accessing data.

DWH will have overall responsibility for study-wide data management. This overarching cohort DMP will be regularly updated and the responsibility for that will lie with the applicant, who will also have responsibility for metadata creation, data security and quality assurance. The SMG will have responsibility for oversight of data governance, including processes for: updating the overarching DMP; data quality control and integrity; and ensuring data security and confidentiality.

Patients will have their date of birth and NHS number collected and this will be stored in a secure purpose built database. Where data linkage to national databases such as NHS Digital, National Cancer registries or Hospital Episode statistics is required, this identifiable information will be passed onto these national organisation to allow data linkage.

Patients who have withdrawn consent will have all data collected up until the point of withdrawal included in the study. This data will be uploaded onto an electronic CRF and included in the analysis of the study. Data will be submitted either directly onto the electronic CRF or onto paper CRF before input into the electronic CRF. In relation to consent for contact, researchers undertaking studies requiring access to identifiable data (e.g.in order to contact patients about participation in a new research study) will be granted appropriate access on the basis of agreement from the study management team and subject to ethical approval and consistent with patient consent .

### 7.4 Use of tumour samples or data by other researchers

Researchers may request to use material from the LARCH study which have been stored in Biobanks for future research.  Researchers will be required to have their own NHS research ethics committee approval for their research projects, and the release of the material must be approved by the LARCH access committee to ensure an appropriate use of samples.  This will be conducted in accordance with a formalised Access Policy and procedure. Access to the tissue collection is available to research groups based in the UK and elsewhere. The application process consists of five stages, which must be completed before samples are provided:

* Completion of an application form available online and provision of any relevant supporting information, for example the outcome of any external review of the proposed project and copies of relevant approvals from an NHS Research Ethics Committee or equivalent body, if available
* Initial consideration by the custodian (DWH) to ensure that the application is related to the prevention, causes, diagnosis, or treatment of cancer and that all necessary supporting information has been provided.
* Determination of the availability of samples or data or an assessment
* Consideration by the SMG for approval
* Where access is approved- agreement to the conditions of access and signing a Material Transfer Agreement (MTA) and payment of a fee to contribute to the costs of running the biobank

Requesters must be employees of a recognised academic institution or NHS organisation or of a commercial research organisation working directly on healthcare related research, products or services. Requesters must be able to demonstrate, through their peer reviewed publications in the relevant research area, or other relevant evidence, their ability to carry out the proposed study.

Researchers who wish to access the LARCH tumour samples or dataset should initially contact the custodian directly giving a brief outline of the proposed study, the methodology to be followed and the number and type of samples required, using an on-line form. The custodian will assess the suitability of the application and respond to the applicant. Applications may be submitted at any time and will be considered in the order in which they are received. The LARCH SMG aims to acknowledge all applications within one week of receipt and to provide a decision within 3 weeks of receiving a full application. Applications to the cohort can be made before funding and ethical approvals are obtained. In these cases, a letter stating the intent to grant access subject to the appropriate conditions will be issued to the requestor. Any ‘letter of intent’ will be valid for 3 months from the date of issue but does not guarantee access to particular samples or data. If the requested samples are not available when funding and other approvals are secured, the custodian will attempt to provide similar samples/data although this will not always be possible and cannot be guaranteed.

On receipt of the full application, the custodian will check to ensure that the requested samples/data are available, that they are surplus to any which have been set aside for ongoing research, and that all required information has been supplied. If any information is missing from the application the requester will be asked to supply this before the application is considered further. The proposed study protocol will be reviewed by the custodian for suitability. If the protocol is not considered appropriate the custodian will contact the requester to explain why this is the case and may suggest improvements. Where appropriate the SMG may request that the application is reviewed by an appropriate external expert- who will be required to sign a non-disclosure agreement. Requesters may request that certain reviewers be excluded. In certain cases they may request that the project is sent for a full review by an NHS Research Ethics Committee. Requesters from academic groups who propose similar studies may be put in touch with a suggestion that they collaborate. If the requesters are not willing to collaborate then both applications will be considered as usual. However, it is very unlikely that access to the collection will be granted for two very similar studies.

Once the conditions for access specified in any ‘letter of intent’ are met, evidence of this (for example letters from funding bodies or Research Ethics Committees) should be submitted to the custodian. If gaining funding or the required approvals will require significant changes to the study, the custodian should be informed as soon as possible together with details of the changes. Depending on the nature of these changes, a new application may be required.

Before access to the cohort is granted, requesters must agree to the conditions of access and return a signed Material Transfer Agreement to the custodian. The requester will be required to cover the costs of retrieving, processing, and dispatching samples. Details of these costs will be provided at the time that an initial enquiry is made. Study titles will be published on the collection website, together with lay summaries and the names of the institutions where the work is taking place. Contact details for the principal investigator of each study will be provided by the custodian upon request. Requestors who do not wish details of their study to be openly available should state this in their application to the collection and give the reason. Samples supplied from the collection must only be used for the purposes stipulated by the custodian and described in the Material Transfer Agreement. Samples or data supplied from the collection may only be transferred to collaborators named at the time of the original application or in subsequent applications and specified in the Material Transfer Agreement or later amendments. Samples will be provided as “linked anonymised/pseudonymised” ie will not have any data which will identify the donor but which can be identified by the custodian by the use of a code. Recipients must agree not to link the samples provided with any other data set without the permission of the custodian.

Recipients must not attempt to identify any individual from the data or samples provided. Should recipients believe that they have inadvertently identified any individual, they must not record this, share the identification with any other person or attempt to contact the individual. IP agreements will be established for the objectives and individual research studies, based on advice from the legal team at The Newcastle upon Tyne Hospitals NHS Foundation Trust. If recipients believe that they have inadvertently identified any individual from the data or samples provided they must inform the custodian and provide details of the circumstances under which this occurred. Unless specified in the Material Transfer Agreement, LARCH waive any rights to intellectual property arising from the use of samples or data provided.

FFPE tissue will consist of tissue blocks held in pathology departments or designated off-site storage facilities utilised by NHS hospitals. In some cases, pathology departments may be unable to release blocks because of concerns that material may be needed for further analysis as part of routine care. In such cases they may be prepared to release tissue sections mounted on slides or “curls”- ie unmounted sections- used for example for DNA preparation. When blocks are available for release pathologists may request that they are returned once material needed for research has been removed. This may not be possible if large amounts of material are needed or if the block is damaged by processing for example, by the removal or cores for the preparation of tissue microarrays. The exact requirements for research will be made clear in the access request.

Once the study agreed with the custodian is complete, any remaining samples must be returned to the biobank. The recipient should notify the custodian in writing that no samples have been retained. Recipients will be required to complete a declaration every 6 months that they have complied with the terms of the Material Transfer Agreement until all samples have been used or destroyed. Recipients found to be in breach of the Material Transfer Agreement will be denied future access to the collection and their institutions and funders informed. All remaining samples must be returned to the biobank.

### 7.5 Sponsor

LARCH will be led by Newcastle University with The Newcastle upon Tyne Hospitals NHS Foundation Trust acting as sponsor. The chief investigator is a full-time dedicated clinical researcher and will be supported by research-experienced co-applicants and a research team employed through grant funding. In participating sites, a principal investigator will be identified. Portfolio adoption will ensure that NIHR CRN research nurses are able to undertake patient recruitment.

### 7.6 Funding

Funding to this study is from The MRC/NIHR Clinical Academic Research Partnership (CARP). Due to the volume of data collection, this study would rely on inclusion on the NIHR portfolio.

## 8. Study Management

LARCH will be coordinated by a trial management group (TMG). The TMG will be chaired by the chief investigator and comprise co-investigators, patient and public involvement (PPI) representation, study manager, research fellow, lead nurse, data managers and digital research engineers. The TMG will advise on matters including appropriateness and sensitivity of patient-facing materials; methods of patient approach, consent and data collection; strategies to maximise retention; interpretation of results; and dissemination to lay audiences. Active involvement of the will help maximise patient acceptability and, hence, recruitment and retention. The study management team will govern all access to data.

### 8.1 Protocol Compliance

A representative group of staff who will be part of the research team at each site will attend a site initiation meeting to ensure compliance with the protocol and allow training in study procedures and data collection methods. The PI at each study site will apply for local R+D approval. The PI will sign a copy of the ethically approved protocol to confirm agreement to carry out all study related tasks in accordance with the protocol. Deviations from protocol will be reported to the study management group.

### 8.2 Responsibilities

All staff involved in the study will undergo GCP training. Day to day delivery will be supported by a research nurse and a research fellow. All investigators and staff with access to data will undergo GDPR training. The responsibilities of the trial team are as outlined below.

*Chief Investigator:*

1. Protocol development
2. Coordination of study
3. Education of study team
4. Ensuring GCP training and governance
5. Support application through approval processes and ethics
6. Data governance and management
7. Data interpretation
8. Contribution to report and papers for publication
9. Ensure uploading of accrual data

*Principal Investigators*

1. Coordination of study
2. Education of study team, hosting of study
3. Ensuring GCP training and governance
4. Data interpretation (including timely assessment of seriousness of adverse events)
5. Review abnormal results (blood and FIT) and act upon them as required. This may be delegated to an appropriate member of the research team
6. Contribution to production of report and papers for publication
7. Ensure uploading of accrual data
8. Overall responsibility for conduct and running of the trial at site
9. Ensuring local governance
10. Applying for R&D approval at their site
11. Recruitment and study conduct according to protocol

## 9. Financing and Insurance

LARCH is funded by the MRC/NIHR Clinical Academic Research Partnership (CARP). Standard NHS indemnity arrangements are in place for the delivery of this study in all recruiting sites.

## 10. Dissemination

Data from the study will be disseminated to participating centres within the study via the Trust’s websites. Additionally, lay summaries will be prepared, posted on the study website and disseminated through websites of individual participating sites and charities. Digital tools for dissemination of research findings will be developed and information disseminated to individuals requesting this.

For academic and clinical dissemination, the results will be submitted for publication in high-impact international peer-reviewed journals and presented to scientific meetings.

Access to anonymised the LARCH dataset by other researchers will be publicised and promoted. The data sharing policy pertaining to this dataset will be made available to researchers.

## 11. Publication Policy

The chief investigator will take responsibility to present and publish the outcomes of the study. The results will be disseminated through peer reviewed national/international journals and learned scientific societies. Additional dissemination for benefit of patients and public will be developed including use of digital media. Recipients working in academic institutions are expected to submit their results to a peer reviewed journal as soon as possible- ideally with open access. Manuscripts should be sent to the custodian prior to submission to establish compliance with the terms of acceptance. The custodian will undertake to keep the contents of submitted manuscripts confidential until publication. If the researchers wish to have this period extended to protect IP, they should discuss this with the custodian. Publications should also be deposited in the UK PubMed Central database within three months of publication. Details of any publications resulting from the use of the samples should be forwarded to the custodian immediately after they become accessible. Details of all publications arising from the use of samples in the bank will be held in a database accessible from the website. Recipients should aim to publish the results of all studies, including negative results, unless this is not possible because of the need to protect intellectual property. If it is not possible to publish negative findings, the manuscript should be submitted to the custodian for inclusion in the collection.

Any publication or presentation using data or samples from the collection should include an acknowledgement using the text: “Samples used in this research were obtained from the LARCH Biobank"