<Trust/Site address 2>
<Trust/Site address 3>
<postcode>
Tel: <telephone number>

Adult Information Sheet for PROTIS

You have been invited to take part in a research study called PROTIS. This is the shortname for, **PRO**ton beam **T**herapy vs **I**MRT for **S**inonasal cancer. PROTIS will compare two types of radiotherapy used to treat sinus cancer: intensity-modulated radiotherapy and proton beam therapy. Before you decide, it is important that you understand why the research is being done and what it will involve.

Please take time to read the following information carefully.

- **Part 1** tells you the purpose of the study and what will happen if you take part.
- **Part 2** gives you more detailed information about the conduct of the study.

You can ask a member of your clinical team if there is anything that is not clear, or if you would like more information.

If you wish you can discuss it with friends, relatives and/or get independent advice via your local Patient Advice and Liaison Service (PALS).

Taking part is voluntary. If you don't want to take part then you don't need to give a reason.

Treatment is for 6-7 weeks (the same duration on or off the trial) and then follow-up as per routine care for up to 5 years.

PROTIS aims to recruit 276 patients, aged 16 years and older, with sinonasal cancer.

How to contact the study team:

If you have any questions about this study please talk to your research team:

- **<Add contact details for PI/RN, i.e. name and telephone number>**

<Trust/Site address 2>
<Trust/Site address 3>
<postcode>
Tel: <telephone number>

Adult Information Sheet for PROTIS

Contents

Glossary

IMRT	Intensity modulated radiotherapy – this is standard of care treatment
PBT	Proton beam therapy
Baseline	This is the first set of assessments that will take place on the trial. It will tell us how you feel/what your health is before we start any treatment
Randomisation	Some of your information will be entered into a computer system which will then assign you either to IMRT arm or PBT arm of the study. This ensures that no person can influence what treatment individual participants receive
Translational samples	This refers to samples that we have requested which will be used to answer important research questions but are separate to the main goals of the trial itself.
MRI (magnetic resonance imaging)	A special technique that takes pictures of internal structures of the body

PART 1: Purpose of the study and what will happen if you take

Why are we doing the PROTIS study?

Cancer of the sinuses (the air spaces in our face around the nose) is a rare disease, which is often found to be quite advanced by the time it is noticed. The treatment for sinus cancer usually involves surgery followed by radiotherapy, but radiotherapy may also be used without surgery. In some cases, chemotherapy may also be used to treat the cancer.

Radiotherapy is an important part, either to treat the cancer itself (where surgery has not been done), or to treat the cancer cells that remain after surgery (without radiotherapy these cells would grow back). Radiotherapy technology has advanced over the last 20 years, and the current treatment using intensity-modulated radiotherapy, has improved cure rates and reduced side effects compared with older techniques.

Proton beam therapy is a newer form of radiotherapy, which may be more effective at treating the cancer or cancer cells to improve the chance of cure. It may also cause less damage to nearby normal structures, resulting in fewer side effects. However, we don't know this, and it is also possible that some side effects may actually be increased by protons.

PROTIS aims to compare proton beam therapy (PBT) with intensity-modulated radiotherapy (IMRT), to see whether or not there is an improvement in cure rates and a difference in long-term side effects.

The study aims to recruit 276 patients, and each participant will be involved in the study for up to 5 years after treatment.

The results from this study will be used to help us improve treatments for patients with sinus cancer.

Why have I been chosen?

You have been invited to take part in this study because you are aged 16 years or older and have been diagnosed with sinus cancer.

Do I have to take part?

No, taking part is voluntary. It is up to you to decide whether or not you want to take part.

If you decide not to take part then you will still receive the usual treatment your hospital offers. Your doctor can provide you with more information on this.

If you decide to take part you can also choose to stop at any time without giving a reason.

The decision you make on whether to take part or not will not affect the standard of care you receive now or in the future.

What will happen to me if I take part?

If you agree to take part, you will be asked to sign a consent form. You will be given a copy of the consent form and this information sheet to keep. A copy of the consent form you have signed will be made available to different teams throughout the trial including LCTC who are co-ordinating the trial (see part 2 for more details).

During your diagnosis several scans would have been conducted and a biopsy taken to confirm the type of cancer you have. We will check and confirm that this study is suitable for you using information in your medical notes and by talking to you about your health.

You may need surgery and/or chemotherapy before radiotherapy. You may also require chemotherapy at the same time as your radiotherapy. The decision for you to have surgery and/or chemotherapy will be made by your usual care team and yourself, whether or not you decide to take part in this study.

Surgery (if required)

Some patients will have surgery before they begin radiotherapy. There are various ways of performing surgery. It can be done through minimal access surgery that use endoscopes up the nose or more open approaches that require incisions on your face or neck to access the cancer. Both types of surgery have been shown to be effective but the decision about which is best for you will depend on the where the tumour is located and how big it is.

Your surgeon will explain which operation will give the best chance of cure and minimise side effects. The surgery itself is part of standard care for treating this disease.

Oncology Visit

As part of your normal treatment, you will attend a visit with the oncology team. At this visit you and the team will discuss what treatment you require above radiotherapy (eg chemotherapy).

If you did not have surgery, then the oncologist will explain the trial and ask you to consent to take part. If you require surgery this will happen after the surgery is complete and you will be asked to reconfirm your consent following a conversation with the oncologist.

Following surgery, there is a small chance that this study is no longer suitable for you. If this is the case, you will not continue in the trial and your clinical team will discuss standard treatment options with you. If the trial is still suitable for you, and you wish to continue, then you will continue with the following:

Baseline tests

In order to understand potential long-term side effects your clinical team will perform a number of tests and assessments prior to you starting radiotherapy. These are called baseline and will let us know how things are before you start treatment. These same tests are then repeated at set times throughout the study to see if/how they change.

These tests include clinical assessment, blood tests, hearing tests, eye examinations, tests to check your sense of smell and for brain function including attention, memory, language, reaction time and perception thinking and memory. You will also be asked to complete a number of questionnaires about your quality of life.

These assessments will require you to attend clinic and some tests such as eye and hearing are performed in different departments. These may need to be performed on different days.

Randomisation

If the study is suitable for you, you will be allocated to receive either intensity modulated radiotherapy or proton beam therapy. There is a 50:50 chance of receiving either treatment, which is decided randomly.

If you are to receive intensity-modulated radiotherapy this will be delivered at your local hospital just as if you were not taking part in the trial.

If you are to receive proton beam therapy, this will be delivered at one of the two NHS proton beam centres in the UK (The Christie, Manchester or University College London Hospital (UCLH), London). Usually this will be the centre closest to your home but other factors are considered for example capacity at the centres.

This will mean traveling to the specialist unit and staying away from home during treatment (up to 7 weeks). Reasonable travel expenses are reimbursed, and the NHS provides apartment accommodation for you and one family member or carer. Your doctor or nurse will provide further information about this.

If you are to receive proton beam therapy, your hospital will send a copy of the consent form to the proton beam centre so they have a record of your consent.

Radiotherapy planning Visit

Before starting treatment, you will attend a planning visit at the treating hospital. This may be at the proton beam centre if allocated to proton beam therapy in the trial. You will meet the members of the team and will attend some clinical appointments; this may occur across several days.

Radiotherapy delivers a focussed treatment and so it is important that you are able to lie still and in the same position for each treatment. To help with this a special mould called a “mask” or “shell” will be made just for you.

During this planning visit you will also have scans, which will be used to plan your radiotherapy treatment. These will include CT and sometimes an MRI scan. During this session you will need to wear your radiotherapy mask. You may also need an injection of what is called a contrast dye. This is given to get better images from the CT scan.

Induction chemotherapy (if required)

If your clinical team decided that you require chemotherapy to shrink your cancer before radiotherapy then you will be scheduled to begin this at your local hospital prior to starting radiotherapy. You will need to

attend the radiotherapy planning session between the first and second cycles of chemotherapy treatments.

Concurrent chemotherapy (if required)

Your clinical team may also decide that you require chemotherapy delivered while you are receiving radiotherapy (concurrent chemotherapy). If this is to happen, you will receive both treatments at the hospital providing your radiotherapy.

Radiotherapy Treatment

The amount of radiotherapy treatment you receive is described in fractions. You will receive 30 to 35 fractions of treatment. This will be delivered once daily (excluding weekends) every week, for 6 to 7 weeks.

During your treatment the clinical team will monitor your symptoms and any side effects. At the immediate end of your treatment, you will have a health status assessment and be asked to complete some questionnaires.

If you are attending a proton beam centre, you will be discharged back to the care of your local hospital for routine follow-up.

Contingency plans

Both forms of radiotherapy are delivered by specialised machines and there may be instances when these machines are out of service. There will be contingency plans in place at the hospital in case this happens during your treatment. This may include either making up for the treatment(s) on another day (for example, by treating you twice on another day, or additionally on a Saturday) or switching your treatment to intensity modulated radiotherapy, while the proton machine is fixed.

After Treatment (follow-up)

After treatment, you will need to attend follow-up visits at your local hospital as part of your routine care (these would happen even if you weren't in this study). As you are taking part in the trial there will be some additional tests and you will be asked to complete questionnaires (detailed in the table). The first visit is 6 weeks after finishing treatment. Then 3, 6, 12, 18 and 24 months after treatment, then once a year for the next 3 years.

Your clinical team may want to see you at other times if they or you have concerns or you have symptoms.

Sample collection

While you are taking part in the PROTIS trial we would like to collect some samples which can be used to answer important research questions. All sample collection is optional, meaning you can say no to this but still take part in the trial.

There are specific consent statements listed on the consent form which you will be asked to complete to document that you have given your permission for these samples to be collected and used. In order to keep a record of this we would also send a copy of this consent form to the GCP Labs.

The samples we would like to collect are listed below and are presented within the table on the following pages.

All participants

We would ask to collect 10mls (2 teaspoons) of blood taken with standard of care samples at your baseline visit.

As part of your diagnosis the hospital will have taken a biopsy from the tumour and then stored it. As part of the trial we ask for your permission to allow the hospital to send this tissue.

Participants undergoing surgery

During surgery to remove your tumour we would like to collect 3 small biopsies of the tumour and a small piece of normal tissue

Recurrence

If your cancer comes back while taking part in the trial, we may request that during surgery to remove the cancer we also collect some biopsies from the tumour.

Details of how samples will be handled and stored are detailed in part 2

Patient entry pathway			
Patients having surgery **not part of trial but provided as standard of care**	**Informed consent**	You will be given time to read this information sheet and speak with the team. You will then be asked to sign the consent form.	Research
	Confirmation of Eligibility	During a clinical visit, the clinical team will review your medical notes (including biopsy and imaging performed as part of your normal care) and speak with you about your health to ensure the trial is suitable for you.	Research
	Pre-surgical assessment	Questionnaire	Research
	Surgery (specific details will be provided by your surgical team)		Standard
	Biopsies taken (if you have provided consent)		Research
	Attend an oncology appointment		Standard
	Reconfirm eligibility and consent	The oncologist will discuss your treatment and the trial with you and ask you to confirm that you wish to continue. There is a small chance that you may be withdrawn from the trial if the oncology team feel this is no longer suitable for you	Research
Patients not having surgery **(at oncology appointment)**	**Informed consent**	You will be given time to read this information sheet and speak with the team. You will then be asked to sign the consent form.	Research
	Confirmation of Eligibility	The clinical oncology team will review your medical notes (including biopsy and imaging performed as part of your normal care) to ensure the trial is suitable for you. They will also state whether you require induction chemotherapy	Research

Pathway for all patients			
Procedure		**Description**	
Baseline	Clinical assessments	Current signs and symptoms of disease and your general fitness	Research
	Questionnaires	List of questions to assess how you are feeling	Research
	Olfactory testing	Testing to see how well you smell.	Research
	Hearing test	Testing to see sensitivity of your hearing – in different department	Both*
	Neurocognitive assessment	Test brain function including attention, memory, language, reaction time and perception	Research
	Blood tests	Pituitary function blood tests (growth hormone, ACTH/cortisol, thyroid and gonadotrophin function)	Standard
	Eye tests	visual acuity, visual fields, OCT, media clarity and ocular alignment/movement assessment – in different department	Both*
Baseline samples optional	Blood tests	Translational bloods	Research
	FFPE Tissue	Tissue taken during your diagnosis is held by your hospital we ask that you gift this to us for research purposes	Research
Randomised to either Standard of Care Therapy (IMRT) or Research Treatment (PBT)			Research
Induction Chemotherapy if required Standard of Care at local hospital			Standard
Radiotherapy planning		Attend the treating centre for planning scans and fitting of a shell to be worn during treatment	Standard
Treatment Weeks 1-7	Radiotherapy	30-35 fractions of radiotherapy daily (with chemotherapy if required)	IMRT standard PBT research
	Reported toxicities	The doctor will record any side-effects you are having as part of the radiotherapy treatment	Research
	Clinical assessments	Current signs and symptoms of disease and your general fitness	Research
End of treatment Week 6 or 7	Questionnaires	List of questions to assess how you are feeling	Research
	Reported toxicities	The doctor will record any side-effects you are having as part of the radiotherapy treatment	Research
	Clinical assessments	Current signs and symptoms of disease and your general fitness	Research

Follow-up after finishing radiotherapy			
6 weeks	Reported toxicities	The doctor will record any side-effects you are having as part of the radiotherapy treatment	Research
	Clinical assessments	Current signs and symptoms of disease and your general fitness	Standard
3, 6, 12, 18 and 24 months	Radiological assessment	MRI Neck/Sinuses (3, 12, and 24 months)	Standard
	Clinical Response assessment	The doctor will record how you have responded to the treatment	Standard
	Reported toxicities	The doctor will record any side-effects you are having as part of the radiotherapy treatment	Standard
	Clinical assessments	Current signs and symptoms of disease and your general fitness	Standard
	Questionnaires	List of questions to assess how you are feeling (3, 12 and 24 months)	Research
	Neurocognitive assessment	Test brain function including attention, memory, language, reaction time and perception (3, 12 and 24 month)	Research
	Blood tests	Pituitary function blood tests (12 and 24 months)	Standard
	Olfactory testing	Testing to see how well you smell done (24 months)	Research
	Hearing tests	Testing to see sensitivity of your hearing (24 months)	Both*
	Eye tests	Visual assessment (24 months) plus fundus fluorescein angiography	Both*
3, 4 and 5 years	Clinical response assessment	The doctor will record how you have responded to the treatment	Standard
	Radiological assessment	MRI Neck/Sinuses	Standard
	Questionnaires	List of questions to assess how you are feeling	Research
	Neurocognitive assessment	Test brain function including attention, memory, language, reaction time and perception	Research
	Blood tests	Pituitary function blood tests (year 5 only)	Standard
	Eye tests	Visual assessment (year 5 only)	Both*

*Both (depending on study arm) – for proton beam therapy, these assessments are routine. We will also do these for patients receiving intensity-modulated radiotherapy, so that we can make comparisons between the two treatments

What is the treatment being tested?

Radiotherapy has been used as a standard treatment of head and neck cancer as well as other cancers for many years. However, the use of radiotherapy is complicated because of the closeness to critical areas, such as the eyes, ears and brain and other nearby structures such as the sinuses themselves, which may be damaged by radiotherapy.

Both Intensity-modulated radiotherapy (IMRT) and Proton beam therapy (PBT) are types of radiotherapy but use different types of radiation to treat the cancer.

A full dose of radiation is usually divided into a number of smaller doses called fractions. This allows healthy cells to recover between treatments. In the PROTIS study, you will receive 30 to 35 fractions of either IMRT or PBT over 6 to 7 weeks.

For both types of radiotherapy, you will need to wear a mask, to help keep the area being treated as still as possible during the radiotherapy. This is to ensure that the treatment is as accurate as possible.

How will I know which treatment I'm going to have?

In research studies we often split patients up into groups to look at how different treatments work. In the PROTIS study patients will be split into two treatment groups at random:

- One group will receive IMRT (standard of care)
- The other group will receive PBT

It is really important that each group in the PROTIS study has a similar mix of patients in it so we know that if one group of patients does better than the other it is very likely to be because of the treatment and not because there are differences in the types of patients in each group.

We use a computer programme that puts patients into groups 'at random' – you might hear this described as 'randomisation' or 'random allocation', but they all mean the same thing. Neither you nor your doctor choose which group you are in.

In the PROTIS study you are equally as likely to be in the group receiving IMRT as you are in the group receiving PBT and your healthcare team will let you know which group you are in.

What are the alternatives for treatment?

IMRT is the usual radiotherapy treatment you would receive, depending on your condition. You doctor will be able to let you know what other treatment options are available for you.

What are the benefits and risks of taking part?

It is known that most patients having radiotherapy will experience some side effects. Part of the PROTIS trial is to understand whether proton beam therapy can reduce the side effects of radiotherapy. At the moment we do not know if this is the case.

Benefits

Although proton beam therapy is a relatively newer form of radiotherapy that may be more precise, cause less damage to the nearby normal structures and may be more effective at treating the cancer or cancer cells to improve the chance of cure we do not know which treatment is best. This is what we are trying to find out.

We hope that the results from the study will help doctors and patients in the future when making decisions about treatment.

Risks

Radiotherapy

The sides effects of either radiotherapy treatment depend on where the radiation is aimed and can include:

Tiredness and weakness

Skin reactions – red, dry, itchy, blistering, peeling

Sore mouth and throat – your mouth and throat are likely to become increasingly sore. The lining may break down (get ulcerated) as you go through your treatment. Painkillers, gels or mouthwashes may be available for you to manage this.

Pain on chewing or swallowing – as your course of radiotherapy goes on, you may have difficulty chewing and swallowing. This is because your mouth and throat might be sore. Your throat is only likely to be affected if you are also having your neck treated. If you experience

this, a liquid diet or feeding tube may help provide the necessary nutrition you need to recover from the treatment.

Dry mouth – radiotherapy to this area can cause damage to the glands that produce your spit (salivary glands). Saliva may become thicker and sticker making it harder to chew and swallow. After the treatment, you may have a temporary dry mouth for a while, but for some people this may be permanent, which can make eating and talking very uncomfortable. You are more likely to get an infection or tooth decay if your mouth is dry. So you'll need to keep an eye on this and have regular check-ups with your dentist. Your doctor may be able to prescribe artificial saliva to keep it moist. This will make you more comfortable.

Change in taste – change in taste may affect your appetite.

Eye problems – your eyes are close to the nose and sinuses. Having radiotherapy to this area sometimes means that your eye is in the path of the treatment.

Change in sense of smell – radiotherapy can damage the cells in your nose that give you your sense of smell.

Changes in hearing – radiotherapy to the nasal cavity or paranasal sinuses can affect your hearing. You may find it hard to hear soft sounds. Or you may have problems to tell different sounds apart.

Changes in your sinuses – you may have inflammation and/or infection of the sinuses that requires pain killers and antibiotics.

Changes in the brain – during treatment you may develop headaches that require treatment with steroids, and in the longer term there may be changes in brain function including attention, memory, language, reaction time and perception (which is one of the things we are monitoring and investigating in the trial)

Changes in your thyroid – radiotherapy to the neck can damage the thyroid gland. If this happens, you will need to take pills to replace thyroid hormones.

Hair loss – radiotherapy causes some hair loss to the area of treatment. It can also cause hair loss on the opposite side of the head. This is where the radiotherapy beam leaves the body (the exit site).

Difficulty opening your mouth – radiotherapy can damage the nerve controlling the muscles which move your mouth. This can make it difficult for you to open it. This is known as trismus. You doctor or nurse may be able to suggest some exercises to help relieve the problem.

Swelling – after radiotherapy, you are at risk of getting swelling called lymphoedema. Lymphoedema in the head or neck area might also cause swelling of your tongue and other parts of your mouth. Tell your doctor if you: have any swelling in the head or neck area or a feeling of fullness or pressure; find it difficult to swallow; or have changes in your voice.

Nervousness – the radiotherapy machines are big and can be loud, so it is normal to sometimes feel nervous, particularly if you also need to wear a mask. Some treatment rooms may be able to play music or audiobooks while you have treatment.

It is important to note that some of these side effects may be temporary and should clear up once the treatment is completed. However, in some cases, the side effects can be permanent. If you experience any of these symptoms, speak to your doctor or nurse who will be able provide you with something to help manage it. The study team's contact details are available on page 1 of this information sheet.

During the trial you will be having test/assessments which tell us about some of the side effects participants may experience. A radiologist will look at MRI scans you have, to check for any signs of changes to the brain which might have been caused by the radiotherapy. The number of times changes are found across all participants will be reported to the trial safety committee.

Radiation Risk

The side effects of radiotherapy are discussed above, however radiotherapy and some of the imaging techniques needed on the trial carry a radiation risk.

This study requires exposures to ionising radiation which would take place as part of routine clinical care. Participants taking part in this study will therefore not be exposed to any additional radiation.

All imaging in the PROTIS trial is in line with standard of care. These procedures use ionising radiation to form images of your body and/or provide treatment and/or provide your doctor with other clinical information.

The radiation dose from the imaging procedures will be very small compared to the dose from the treatment you are receiving.

Ionising radiation may cause cancer many years or decades after the exposure. Taking part in this study will not significantly alter the chance of this happening to you.

Pregnancy

Women of childbearing potential should not become pregnant during treatment in the study and for 4 months after completion of all treatment. An adequate method of contraception (defined as barrier methods in conjunction with spermicide, approved contraceptive implants, long-term injectable contraception or intrauterine hormonal devices) must be used during treatment in the study and for 4 months after completion of all treatment.

Men taking part in the trial should use an acceptable method of contraception (defined as barrier methods of contraception in conjunction with spermicides) during treatment in this study and for 4 months after completion of treatment.

In the very unlikely event that a pregnancy occurs patients should report this to their treatment centre immediately. Please not that pregnancy testing is not performed as part of the trial.

Testing possible side effects

The majority of tests that you will undergo to see whether your treatment has caused any side effects are tests that are routinely performed without any side effects.

Eye Tests

This will be carried out within an Ophthalmology (Eye) Department. In order to complete all the tests you are likely to be in clinic for longer than 1 hour.

Various different methods/instruments/devices will be used to test different aspects of your vision. Some of the tests may cause minor discomfort during the procedures, others will require that drops are added to your eye which will temporarily affect your vision (you will not be able to drive for several hours after).

At 24 months a fundus fluorescein angiography (a procedure that will allow us to examine the back of your eye) will be performed. This involves a small amount of dye being injected into your arm. It then travels to your eye and highlights the blood vessels for us to examine and photograph. This test will take around 15mins.

Afterwards your skin and urine may be orange in colour. This should disappear after around 48hours. The side-effects of this dye injection are rare but can cause nausea or being sick usually immediately after the injection, or an allergic reaction that is usually a minor rash or itching sensation. Extremely rarely, this can cause a severe allergic reaction or anaphylaxis and the teams looking after you are well equipped to deal with this emergency. It is important to tell your medical teams whether you have had any similar reactions in the past.

Hearing Tests

Will be performed in an Audiology department and should not cause any side effects.

Brain Function tests

These tests involve completing short tasks which are designed to test attention, memory, language, reaction time and perception. They will be performed in the presence of medical staff and should not cause any side effects.

Sense of Smell tests

No expected side effects

Surgery and Chemotherapy

For some patient's surgery and/ or chemotherapy are an important part of treatment. Whether you need these treatments will be decided by your doctors and will be the same whether you are taking part in the study or not. Both surgery and chemotherapy carry risks and side effects. These will be discussed with you separately.

Blood Tests

Blood samples will be collected during the study, which may result in mild pain, bruising or redness at the needle site. These will be minor and should clear-up after a few days.

What happens if I change my mind?

If at any point you decide to stop taking part in the study you will still receive treatment and the follow up offered by your hospital.

If you do decide to stop taking part we will ask you if you would like to:

- continue to complete follow up visits for the study **or**
- stop taking part with no more study visits.

Information on how we will handle your information and samples in the event of you withdrawing is detailed in Part 2 of this Information Sheet.

What happens if I become more unwell?

Sometimes people can get more ill while they are taking part in a trial (both physical and mental health which may be unrelated to this trial). The clinical team will advise if at any point they feel you should be withdrawn from follow-up visits/ the trial.

Some changes in your health may mean that you become unable to communicate your wishes to us to remain on the trial (lack capacity). If this happens, your doctor will withdraw you from taking part in further trial related activities. We will continue to collect follow up data about your cancer and its treatment from your hospital records.

We will keep the data and the biological samples that we have already collected from you in a pseudo anonymised format, but we will not collect any more data or samples from you. We will continue to collect follow up data on your cancer and its treatment from your hospital records during the trial period.

What if new information becomes available?

Sometimes during the course of a research project, important new information becomes available about the treatment that is being studied. If this happens, your doctor will tell you about it and discuss with you whether you want to or should continue in the study. If you decide to withdraw your doctor will make arrangements for your care to continue. If you decide to continue in the study you will be asked to sign an updated consent form.

On receiving new information your doctor might consider it to be in your best interests to withdraw you from the study. He/she will explain the reasons and arrange for your care to continue.

If the study is stopped for any other reason you will be told why and your continuing care will be arranged.

What happens when the study stops?

In the study, you will receive either intensity-modulated radiotherapy or proton beam therapy for a defined treatment course of 6-7 weeks. There are no further study treatments. We will follow-you up as part of the study for up to five years and a minimum of two years.

It is intended that the results of the study will be presented at conferences and published in medical journals so that we can explain to the medical community what our research results have shown. They may also be used to apply to the regulatory authorities to make the drug widely available and/or for research related to the development of pharmaceutical products, diagnostics or medical aids. Confidentiality will be ensured at all times and you will not be identified in any publication.

Any information derived directly or indirectly from this research, as well as any patents, diagnostic tests, drugs, or biological products developed directly or indirectly as a result of this research may be used for commercial purposes. You have no right to this property or to any share of the profits that may be earned directly or indirectly as a result of this research. However, in signing this form and donating tissue and/or blood samples for this research, you do not give up any rights that you would otherwise have as a participant in research. All data derived from this study will be archived for a minimum of 5 years and gifted for future research thereafter.

What if there is a problem?

Any complaint about the way you have been dealt with during the study or any possible harm you might suffer will be addressed. Detailed information is given in Part 2 of this information sheet.

Will my taking part in the study be kept confidential?

Yes. All the confidential information about your participation in this study will be kept confidential. Detailed information on this is given in Part 2.

PART 2: Detailed Information about the conduct of the study

Who is running the study?

The Christie NHS Foundation Trust is the Sponsor of this study and is responsible for managing it. They are based in United Kingdom. They have asked that the day to day running of the study is carried out by a team based at the Liverpool Clinical Trials Centre (LCTC, part of the University of Liverpool).

Responsibility for managing the collection of the study samples is with the University of Liverpool GCP Labs.

The study has been reviewed by the Health Research Authority and the National Research Ethics Service Committee to make sure that the study is scientifically and ethically acceptable.

This study is funded by Cancer Research UK, using a donation from The Taylor Family Foundation. Through this funding, you can claim back the cost of travel (standard ticket) to the proton beam centres.

If you are allocated to receive proton beam therapy then accommodation will be provided (via the NHS) for you and one relative/carer during treatment at the proton beam centre.

Additional funding was provided by North West Cancer Research to cover some of the costs associated with the delivery of neurocognitive testing.

Your doctor will not receive any personal payment for including you in this study. The hospital may receive additional funding to help with any extra costs that supporting this study might incur.

How will my information be collected and handled?

The Christie NHS Foundation Trust is the Data Controller for this study and will need to use information from you and from your medical records for this research project.

This information will include your

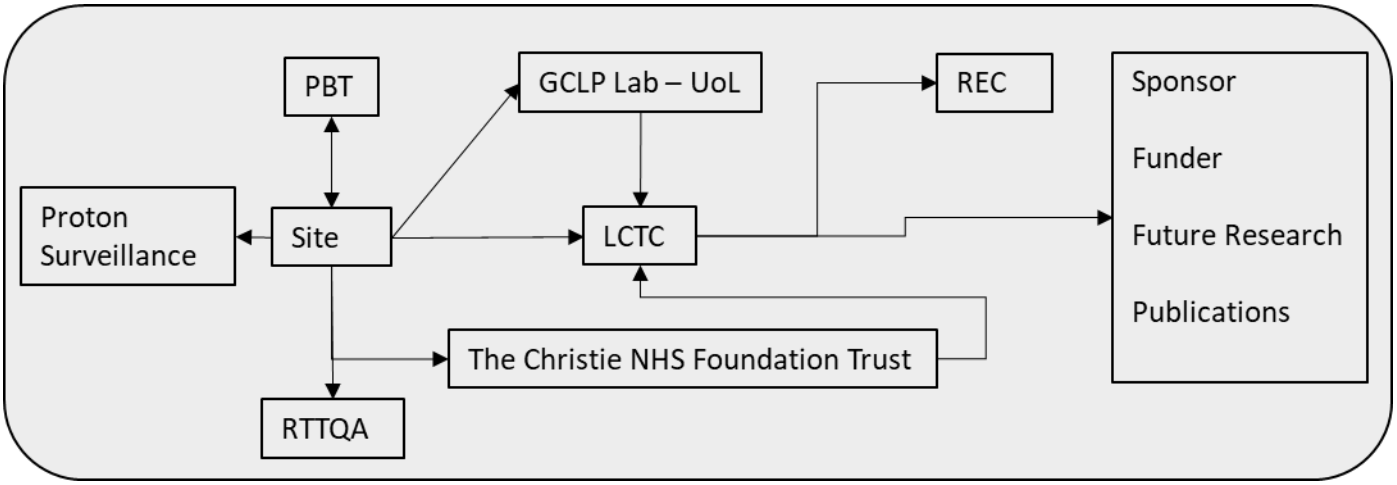
- Initials
- NHS number
- Full name

People will use this information to do the research or to check your records to make sure that the research is being done properly.

Individuals from The Christie NHS Foundation Trust, the LCTC, The National Proton beam centres (Manchester and London), members of the Radiotherapy Trials Quality Assurance (RTTQA) group, The University of Liverpool, auditors from the Sponsor, and regulatory organisations may look at your medical and research records to check the accuracy of the research study.

People who do not need to know who you are will not be able to see your name or personal data. Your data will have a code number instead.

We will notify your GP that you will be taking part in the study for their information.



Main data from site to LCTC - Data will be sent from hospital (including proton beam centres) to the LCTC.

Medical data between site and proton beam centre - If randomised to PBT, medical data and consent will be sent via referral portal (this is an NHS pathway). Once treatment has ended patient will be discharged back to the local site.

Pathology review – as part of the trial your hospital will send a piece of your cancer (taken during biopsy) to be reviewed. The pathology report from your hospital will be sent with it but your person information will be removed and the trial ID added instead

Sample data from site to labs – blood and tissue samples, will be sent from your hospital to the University of Liverpool GCP labs.

Medical data from site to RTTQA – data used to design your treatment plan will be sent to Radiotherapy Trial Quality Assurance (RTTQA). The data is uploaded via the trial specific RTTQA portal and all patient identifiers will be removed and replaced with trial ID at this point. We need to send this information to RTTAQ to make sure that radiotherapy given to patients is consistent across the different hospitals taking part. RTTAQ is an independent group of experts funded by National Institute for Health and Care Research (NIHR). Data required includes; scans with the associated reports and a brief clinical history.

Medical data from site to Radiologist at The Christie to LCTC - An independent radiologist will review data from MRI scans at set time points. The overall findings will be reported to the safety oversight committee via LCTC.

Medical data from site to proton clinical outcome unit (PCOU) - As part of a national surveillance program clinical outcomes from PBT are collected for all patients (NHS and clinical trials). Data collected as part of the trial will be sent as per a data sharing agreement between LCTC and the PCOU.

We will keep all information about you safe and secure. Once we have finished the study, we will keep the data for a minimum of 5 years, so we can check the results. We will write our reports in a way that no-one can work out that you took part in the study.

What are my choices about how my information is used?

You can stop being part of the study at any time, without giving a reason, but we will keep information about you that we already have.

If you choose to stop taking part in the study, we would like to continue collecting information about your health from central NHS records/ your hospital/ your GP. If you do not want this to happen, tell us and we will stop.

In some cases, however we may need to continue to collect limited information about any side-effects of the study treatment you may experience or pregnancies. We will only do this where we are required to do so by law.

We need to manage your records in specific ways for the research to be reliable. This means that we won't be able to let you see or change the data we hold about you.

Information sharing for other research

When you agree to take part in a research study, the information about your health and care may be beneficial to researchers running other research studies in this organisation and in other organisations. These organisations may be universities, NHS organisations or companies involved in health and care research in this country or abroad. Your information will only be used by organisations and researchers to conduct research in accordance with the UK Policy Framework for Health and Social Care Research, or equivalent standards**.**

If you agree to take part in this study, you will have the option to take part in future research using your data saved from this study.

This information will not identify you and will not be combined with other information in a way that could identify you. The information will only be used for the purpose of health and care research and cannot be used to contact you or to affect your care. It will not be used to make decisions about future services available to you, such as insurance.

Where can I find out more about how my information is used?

You can find out more about how we use your information:

- at the LCTC website: www.lctc.org.uk
- at www.hra.nhs.uk/information-about-patients
- by asking one of the research team
- by sending an email to <site **email**>, or
- by ringing us on <site **phone number**>
- in the Health Research Authority leaflet available from www.hra.nhs.uk/patientdataandresearch

By contacting the The Christie NHS Foundation Trust Data Protection Officer:

Data Protection Officer
The Christie NHS Foundation Trust
Wilmslow Road
Manchester
M20 4BX
Telephone number: 0161 446 3043
Email: the-christie.dpo@nhs.net
https://www.christie.nhs.uk/about-us/data-protection

If you are not happy with the way your information is being handled, or with the response received from us, you have the right to lodge a complaint with the Information Commissioner's Office at Wycliffe House, Water Lane, Wilmslow, SK9 5AF (www.ico.org.uk).

What will happen to the blood and tissue samples I give?

With your consent, during the trial we will be collecting blood and biopsies from you and asking your hospital to send the biopsy taken during your diagnosis (details in part 1). All samples will be sent directly from site to Liverpool GCP labs, who will manage and store all samples collected during the trial.

The biopsy from your diagnosis (FFPE tissue) is first needed for pathology review alongside the report created during your diagnosis. These will be reviewed by a Pathologist based at Manchester University NHS Foundation Trust. The tissue will then be stored at the GCP Labs.

The biopsies and blood samples sent from sites will be prepared so that they can be stored at the GCP Labs.

The samples will be coded and the researchers will not be given information they do not need to carry out the tests and analyse the results. Coded is not the same as anonymous. It will be possible to use the codes to identify that a result is from your sample. However, we do not plan to do this unless there is a good reason to do so. We will maintain this information so that we can properly manage the samples. For instance, sometimes we may need to update our record of your clinical details to help us interpret the results of tests.

If you choose to withdraw from the study, we won't collect any more samples from you, but we will continue to store and use the samples we have already collected. If you do not want us to do this, please let us know and we will stop. It may however not be possible to destroy some of your samples if they have already been used up as part of the study analysis.

Samples for future research

With your permission, we would also like to keep any samples that still remain at the end of the trial so they can be used in future research.

If you agree, coded samples will be stored at Liverpool GCP Labs during the trial and then in LCTC Post Trials Bank, once the trial has ended.

Some of the data we collect about you in this study will be provided alongside your samples – this too will be coded. These researchers work closely with other scientists in the UK and elsewhere and may transfer your samples to these research collaborators for use in future scientific studies.

These samples may be used for translational research, including testing of the genetics of this cancer, how radiotherapy affects cancer cells, how the cancer affects the human immune system and how we might predict response to treatment or identify potential new treatments.

The samples will be kept in a secure place until we need them; nobody outside of the study will have access to **any** confidential information that you give to us. Confidential details (such as your name, and GP details) will be kept locally and not made available to collaborators. If you decide you do not want to gift your samples, they will be destroyed at the end of the study.

If you choose to withdraw from the study, we won't collect any more samples from you, but we will continue to store the samples we have already collected and these will be made available to future researchers. If you do not want us to do this, please let us know and we will stop where possible. It may however not be possible to stop this where the samples have already been provided to researchers.

Sub-study – Liverpool and Manchester ONLY

Alongside the main PROTIS trial, we will be conducting a sub study which will collect tissue and blood in order to answer important research questions linked to the body's immune response to the different types of RT.

You will be invited to take part in this sub study if you;

- Have consented to take part in the main PROTIS trial
- You are scheduled to undergo surgery to remove your cancer within either Liverpool University Hospitals NHS Foundation Trust or Manchester University NHS Foundation Trust.

Do I have to take part?

If you decide not to take part in this sub-study you can still participate in the main PROTIS study.

What will happen to me if I take part?

If you agree to take part, you will be asked to sign a separate consent statement at the end of this form. This sub-study requests to collect biopsies and additional blood samples as you take part in the main study described in this document.

During the surgery to remove your cancer, small biopsies will be collected (this will replace the biopsy requested in the main study).

Additional blood samples (10mls or 2 teaspoons) will also be collected at 6 different times during the trial, as shown below;

- At surgery
- Week 1 of RT
- Week 3 of RT
- Week 6 of RT
- 6 weeks after RT
- 3 months after RT

All the samples will be transferred to Liverpool GCP Labs for processing and storage until required by the research team.

What if there is a problem?

If you have a concern about any aspect of this study, you should ask to speak with one of your research team who will do their best to answer your questions.

If you remain unhappy and wish to complain formally, you can do this by contacting local NHS Patient Advice and Liaison Service (PALS) or equivalent. Members of your local hospital team should be able to provide this information to you.

Every care will be taken in the course of this clinical study. However, in the unlikely event that you are harmed by taking part in this research project, there are no special compensation arrangements. If you are harmed and this is due to someone's negligence, then you may have grounds for a legal action for compensation against the NHS Trust where you are being treated but you may have to pay for your legal costs. The normal National Health Service complaints procedures will still be available to you.

If you have private medical insurance, you should tell your insurance that you are taking part in research. They will let you know if it affects your policy

Thank you for taking the time to read and consider this information sheet. Should you decide to take part in the study, you will be given a copy of the information sheet and a signed consent form to keep.

<Trust/Site address 1>
<Trust/Site address 2>
<Trust/Site address 3>
<postcode>
Tel: <telephone number>