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PROTIEUS

PATIENT INFORMATION SHEET (Main Study) Part 2

A Randomised Phase 2 Trial Comparing Proton versus Photon Based Neoadjuvant Chemoradiation, followed by standard therapy, in Oesophageal Cancer

IRAS No.: 329646

Part 2 Contents

1. Patient Video

To find out more about the PROTIEUS trial you can watch the PROTIEUS patient video online:

www.ctc.ucl.ac.uk/QR/protieus-1.html

2. Why are we doing this study?

Patients with cancer of the oesophagus/gullet (food pipe) are usually treated with systemic anti-cancer treatment (SACT) (including chemotherapy and immunotherapy), radiotherapy and surgery.

Your hospital doctor is considering using chemotherapy and radiotherapy before surgery to treat your cancer. This combination has been proven to be effective treatment but may cause more complications or side effects after surgery (than chemotherapy alone) which usually affects the lungs and heart.

This study is trying to find out if a new type of radiotherapy called 'Proton Beam Therapy' can reduce the severe complications such as those affecting the lungs and heart after chemotherapy, radiotherapy and surgery to remove the oesophagus, when compared to standard radiotherapy with chemotherapy and surgery.

There is no suggestion that proton beam therapy is more or less effective than standard radiotherapy. We would like to find out if using proton beam therapy will actually reduce the complications or side effects of surgery, and that is why we are running this study.

3. What is the difference between the two types of treatment in this study?

The standard radiotherapy used to treat your type of cancer is called intensity modulated radiotherapy (IMRT). This uses high energy beams of radiation (X-rays) to destroy cancer cells. It is a targeted treatment, but healthy tissues near the oesophagus (food pipe) such as the lungs and the heart can be damaged by X-rays as they enter and leave the body. This may result in a higher number of complications to the lung and heart after surgery to remove the oesophagus.

What is Proton Beam Therapy?

Proton beam therapy is a type of radiotherapy that uses high energy proton beams (tiny particles found in atoms) to treat cancer.

During your proton beam therapy, you will be placed inside a machine called a proton accelerator, where a beam of protons is carefully aimed at the tumour. With this type of radiotherapy, there is less radiation dose to healthy tissues beyond the tumour as the protons travel to the desired depth in the body (at the site of the tumour). We know from the use of proton beam in other countries (for example, the United States) that it is a safe treatment, with similar cure rates compared with standard radiotherapy (IMRT), and it is thought to cause less damage to healthy tissues.

4. Your Invitation

You have been diagnosed with oesophageal cancer, and your hospital doctor has advised you to have radiotherapy as part of your standard treatment, therefore you have been invited to take part in the PROTIEUS study.

If you decide to take part in the trial, you will be randomly assigned to receive either standard radiotherapy or proton beam therapy with chemotherapy. All patients will undergo routine surgery. After surgery, if you still have some cancer cells in the surgical specimen removed (residual disease), you will be given immunotherapy treatment for up to 12 months. If you do not have cancer cells in the surgical specimen you might be given more chemotherapy as standard.

A total of 170 patients are required in the study, with 85 patients in each group from hospitals in England and Wales. This means you have a 50/50 chance of being in either group.

5. What will happen to me if I decide to take part?

All patients in both treatment groups will need to have a number of routine examinations checked to see if you are suitable to enter the study. You would have these examinations whether you are on the study or not, to help determine the extent of your cancer.

These may include:

- A physical examination
- A CT scan (computerised tomography)
    - This is a specialised X-ray test which gives clear pictures of the inside of your body.
- A PET scan (positron emission tomography)
    - This scan uses a special radioactive dye (radiotracer) to check if your cancer has spread to other parts of your body.
- Endoscopic ultrasound (EUS)

  - This combines two types of tests - endoscopy and ultrasound.
  - The doctor or nurse uses a thin flexible telescope (endoscope) with an ultrasound probe attached to look inside your food pipe.
  - Ultrasound uses soundwaves to get a detailed picture of any abnormalities seen.
  - A tissue sample (biopsy) may be taken during this procedure.
- Laparoscopy
  - This is keyhole surgery that will be used to assess the extent of cancer near your stomach and liver.
- Cardiac Function Testing
  - Echocardiogram
    - This scan uses soundwaves (ultrasound) to look at your heart and other nearby blood vessels.
  - MUGA (Multi-gated Acquisition scan)
    - This scan uses a radioactive dye (radiotracer) and a special camera to take pictures of your heart as it pumps blood.
  - An Electrocardiogram (ECG) to assess your heart rhythm
    - This test measures the electrical impulses that make your heartbeat and can tell your doctor how well your heart is working.
  - A cardiopulmonary exercise test (CPET) lets your doctor see how your lungs, heart and muscles react together when you exercise. During the test, you will walk on a treadmill and we will measure how much air you breathe, how much oxygen you need and how fast your heart is beating when you exercise.

At the end of this Patient Information Sheet, there is a summary of what you can expect if you participate in the PROTIEUS Study. You may find this helpful to track your involvement throughout the trial (page 23).

6. Study Timeline

Screening:

If you agree to take part in the PROTIEUS study, you will need to sign a consent form. You will then enter a screening period to check if you are suitable to enter the study.

Randomisation:

Once all the screening tests are complete, your hospital doctor will discuss the results with you and confirm if it is suitable for you to proceed with the study.

Which type of radiotherapy you receive in the study; proton beam therapy or standard radiotherapy; is not decided by you, your hospital doctor, or any other person. The choice is made at random by a computer, at the time you enter the study. This process is called ‘randomisation’ and you will be given a unique study number. If one group does better than another group, it is more likely to be because of the treatment, and not because the patients in one group are somehow different to those in the other group. If you join this study, you

will receive either standard radiotherapy or proton beam therapy together with SACT (chemotherapy +/- immunotherapy) before surgery.

In the PROTIEUS study the randomisation will mean that you have an equal chance of getting proton beam therapy or standard radiotherapy. It is important to remember that we do not know which treatment is better; that is the purpose of the study.

Whichever group you are randomised to, you will receive the best possible care and regular monitoring by your hospital clinical care team.

Your hospital doctor will give you a contact card that you must carry with you at all times. This will contain contact details for your hospital doctor and study team. It also gives information about the study for other health care professionals who may see you for other reasons while you are on the study.

Trial Treatment:

Group 1 - Standard Radiotherapy:

Patients in this group will be given 15 daily doses of standard radiotherapy to the oesophagus (food pipe), once a day, Monday to Friday, for 3 weeks. Your hospital doctor will perform a blood test to check which standard of care chemotherapy treatments will be most suitable for you. Chemotherapy will either be given as 2 weekly sessions or 4 sessions given every 2 weeks (usually on a Monday). Immunotherapy may also be given every 2 weeks with the chemotherapy. Chemotherapy will then continue for 3 more weeks with the radiotherapy. In total, either 5 weeks of chemotherapy will be given or 7 chemotherapy treatments will be given over 11 weeks. All visits for your chemotherapy and radiotherapy treatment, immunotherapy and surgery will take place at your local hospital.

Group 2 - Proton Beam Therapy:

Patients in this group will be given 15 daily doses of proton-beam radiotherapy to the oesophagus (food pipe), once a day, Monday to Friday, for three weeks. Your hospital doctor will perform a blood test to check which standard of care chemotherapy treatments will be most suitable for you. Chemotherapy will either be given as 2 weekly sessions or 4 sessions given every 2 weeks (usually on a Monday). Immunotherapy may also be given every 2 weeks with the chemotherapy. Chemotherapy will then continue for 3 more weeks with the radiotherapy. In total, either 5 weeks of chemotherapy will be given or 7 chemotherapy treatments will be given over 11 weeks. The first two or 4 cycles of chemotherapy and immunotherapy will be given in your local center. The final three cycles of chemotherapy will be given at the proton beam center where you will have your proton beam therapy.

The proton beam therapy will be delivered at either University College Hospital in London or The Christie Hospital in Manchester. You will need to attend for a visit 2-3 weeks before starting proton beam radiotherapy for your hospital doctors to plan your radiotherapy and to start your chemotherapy treatment. You will then return to your local hospital for surgery.

Figure 1: Summary of the usual timings of SACT and radiotherapy before surgery

	Treatment				
	Week 1	Week 2	Week 3	Week 4	Week 5
Radiotherapy/Proton Beam Therapy					
Chemotherapy					

Or

	Treatment										
	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Week 9	Week 10	Week 11
Radiotherapy/Proton Beam Therapy											
Chemotherapy											
Immunotherapy											

Surgery:

You will have surgery to remove part of the oesophagus as routine treatment/standard of care and not as part of the trial. Your hospital doctor will explain to you how your surgeon will do your operation. Your study nurse or the research team will also explain to you how you should prepare before your operation, what will happen on the day of your surgery and after surgery how you will feel and how to look after yourself.

Immunotherapy:

You might also be offered additional immunotherapy treatment after your surgery as part of standard of care.

The immunotherapy drug is given as an IV infusion (drip into your veins) every 2-6 weeks. The infusions should last no more than 2 hours and will usually be administered as an outpatient, that is, you will not need to stay in the hospital overnight.

Chemotherapy after Surgery:

You might be offered additional chemotherapy treatment after surgery as part of your standard of care treatment.

The chemotherapy is given as an IV infusion (drip into your veins) every 2 weeks for 8 weeks. The infusions should last no more than 2 hours and will usually be administered as an outpatient, that is, you will not need to stay in the hospital overnight.

Video:

The Christie have produced a video overview of patients receiving proton beam therapy and this shows what you can expect if you are randomised to proton beam therapy, which can be found at the following link or scanning the QR code below:

https://youtu.be/PSrpfLmxwu0?si=qEwLZwXAj-tKAvZA

How many times will I need to visit the hospital?

You will be seen regularly by your hospital doctor and/or nurse/radiographer during your treatment. This is so that they can assess the effectiveness and side effects of your treatment.

- During chemotherapy and radiotherapy treatment you will be assessed every 1-2 weeks.
- You will then be assessed at your local hospital 4-6 weeks after completing chemotherapy and radiotherapy and then, if suitable, have surgery.
- 4-6 weeks after your surgery you will be assessed at your local hospital to check how you are recovering and whether you are suitable for immunotherapy treatment and/or more chemotherapy treatment.
- You will be seen for follow-up assessments at your local hospital at 3, 6, 9 and 12 months after surgery.
    - You will have a CT or PET scan at the 3, 6 and 12 month visits to check the effectiveness of your treatment.
- If you receive chemotherapy after surgery you will attend your local hospital every 2 weeks for 8 weeks (4 visits).
- If you receive immunotherapy, you will also be assessed approximately 1 month after completing your immunotherapy treatment.
- We will then collect information about your health and cancer status by accessing your NHS medical records for up to 2 years. You will not need to make any extra visits to the hospital for this research during this time.

Summary:

- If you decide you want to take part in this study, you will be asked to sign a consent form to show that you agree to take part.
- You will have tests to make sure you are able to take part and are generally fit enough to take part.
- Most of these tests will be the same as what you would normally have as part of standard of care treatment.
- If it is okay for you to proceed with the study, you will be randomly allocated to your trial treatment, either standard radiotherapy or proton beam therapy with chemotherapy.
- After completion of chemotherapy and radiotherapy (5-11 weeks total), you will have routine surgery.
- After surgery, you might be offered chemotherapy treatment for 8 weeks as standard of care treatment.
- After surgery, you may be given immunotherapy treatment for up to 1 year as standard of care treatment.
- After surgery, you will be seen for follow up visits at 3, 6, 9 and 12 months.
- Throughout treatment and follow-up, you will have a series of test/assessments to assess the effectiveness and side effects of your treatment.

Planning your radiotherapy treatment:

To ensure your radiotherapy treatment is as effective as possible, it has to be carefully planned by your hospital doctor and other specialised staff including radiographers and physicists.

- If you are treated with proton beam therapy, you will visit the NHS proton centre in Manchester or London for one planning visit (for 1-2 days) before starting treatment).
- You will then return 2-3 weeks later for the duration of the treatment (approximately 3 weeks).
- If you are treated with standard radiotherapy, the planning visit before starting treatment (and all your radiotherapy treatment) will be at your local centre.

What does radiotherapy planning involve?

The practical aspects and experience for patients are similar whether you receive proton beam therapy or standard radiotherapy. You will have a visit to the radiotherapy department to plan your radiotherapy treatment.

- You will have a CT scan of the oesophagus area to be treated. During the CT scan you will require an injection of an iodine based ‘contrast’. This will help to highlight the cancer and plan your treatment.
- Radiographers will help you get into the right position for your scan. They may use a firm cushion called a vacbag or a radiotherapy mould (shell) to help keep you still. In

some cases, they may use a corset-type belt to reduce the amount of movement associated with breathing to help improve treatment accuracy.

- At the same time the radiographers will take measurements from you for planning your treatment. The session will take about 45 minutes. All of the planning procedures are part of the routine care for patients receiving radiotherapy to the oesophagus.
- Before treatment, you will also meet other members of the team, for example your key worker, specialist nurse and dietician.

7. What happens during my treatment?

Each radiotherapy treatment session will take approximately 20-45 minutes, as the radiographer needs to get you into the correct position on the couch and make sure that you are comfortable before treatment begins. The total amount of time is longer for proton beam therapy than standard radiotherapy. This is because standard radiotherapy is usually delivered in a continuous circle (or 'arc'), whereas proton beam therapy has up to 3 separate beam positions. Usually, the whole process for each treatment will take approximately 20 minutes for standard radiotherapy (IMRT) and 45 minutes for proton beam therapy. **You will not feel anything, as it is similar to having an X-ray scan.**

For proton beam treatment the planning scan might be repeated during radiotherapy to confirm that there are no changes (such as shrinkage) in the area of the tumour treated.

8. Will I be asked to do anything else?

Filling out questionnaires:

We are asking patients in the PROTIEUS study to complete some online questionnaires relating to your quality of life and your health care use.

An email or text message will be sent to you inviting you to complete these questionnaires, including a link to complete these directly via a computer or smartphone. In order to send these messages, your hospital will securely share your contact information (name, mobile telephone number and/or email address) with third parties. These third parties may be in regions outside of the UK and EU/EEA where data protection laws have different levels of protection to those in the UK and EU/EEA. They will be aware of the study name but will not have access to your health data, and are legally required to keep your information safe, secure and confidential.

Figure 2 shows how many questionnaires you will be asked to complete throughout the study and at which timepoints these will be required. Each questionnaire booklet should take between 5 and 40 minutes to complete. The information you provide in the questionnaire forms will be treated in the strictest confidence.

Donation of Blood and Tissue samples for research:

There are two main types of cancer of the oesophagus/gullet, called oesophageal adenocarcinoma and oesophageal squamous cell carcinoma. We are asking all patients in the PROTIEUS study with the adenocarcinoma type of oesophageal cancer to consent to donate some blood and tissue samples for use in this research. If you are willing to take part, we will ask you to consent to this at the beginning of the study.

- **Tissue samples:** we will ask you to donate tissue that is left over from your tissue (biopsy) sample when you were diagnosed and/or during surgery). You will not need to have any extra biopsies for this study.
- **Blood samples:** we will ask you to donate blood samples up to a maximum of 10 times over a period of 2 years.
- **Figure 2** shows at which timepoints samples will be taken for research.

You do not have to consent to donating blood or tissue samples for research. However, if you do, it will help us to understand more about oesophageal cancer, radiotherapy and immunotherapy and may benefit patients having radiotherapy treatment for oesophageal cancer in the future.

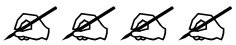
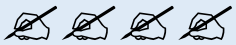
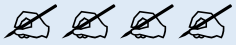
What will happen to the samples I give?

The tissue and blood samples collected for research in this study will be sent to a laboratory in the UK, and used for research to help scientists learn more about oesophageal cancer and radiotherapy treatment. Your samples will be labelled with your initials and unique study number which we will provide to you when you enroll onto the study. We will make all reasonable efforts to ensure that the researchers abide by rigorous standards of conduct.

It is possible in the future that your tissue and blood samples will be sent to other laboratories in the UK for analysis. All laboratories will store these samples securely and they will be destroyed within 1 year after the end of this study. The use of your samples for future research is optional and you do not have to consent to this.

Figure 2: Summary of tissue and blood samples and questionnaires for the PROTIEUS study.

Study visit	Research tissue sample	Research blood samples	Patient questionnaires
Pre-treatment			
Pre-Chemotherapy			
Week before radiotherapy starts			
Completion of Chemotherapy & radiotherapy			

Surgery			
Follow-Up: Month 1			
Follow-Up: Month 3			
Follow-Up: Month 6			
Follow-Up: Month 9			
Follow-Up: Month 12			
Completion of Chemotherapy or Immunotherapy treatment			
If your cancer returns			

Key:

 = 1 blood sample (less than 1 teaspoon of blood)

 = 1 blood sample (approximately 4 teaspoons of blood)

 = 1 quality of life questionnaire/healthcare questionnaire

 = 1 routine tissue sample

9. What are the possible advantages & disadvantages of taking part in this study?

Advantages:

We cannot promise the study will help you, but we hope the information we receive from you taking part in this study will help improve our knowledge of treating oesophageal cancer, which will benefit the treatment of people with oesophageal cancer in the future.

Disadvantages:

Travel/accommodation:

Proton beam therapy is a highly specialised service, provided by the NHS at The Christie NHS Foundation Trust in Manchester and UCLH. If you live outside Manchester or London and receive proton beam therapy as part of the study, it means you will have a long distance to travel and be away from home for 3 weeks of your treatment. A family member or carer can come with you, and you will be supported by a team of doctors, nurses and allied professionals at the proton beam centres. If you do not live near the NHS proton centre, you

may be provided with free accommodation near to the proton centre. However, it is something to be considered carefully before agreeing to take part. Further information will be provided separately if this is applicable to you. We are not able to reimburse any travel costs you incur.

Proton Beam Therapy:

Proton beam therapy is a standard treatment in other countries (for example, USA) for treatment of oesophageal cancers. In the UK, proton beam therapy is routinely used in various cancers affecting children or young adults (less than 24 years old) who require radiotherapy. There is no suggestion that proton beam therapy would be less effective than standard radiotherapy. However, it is not clear whether proton beam therapy for oesophageal cancer reduces complications after surgery and improves long-term outcomes for patients, which is the reason we are doing this study.

10. What are the side effects of any treatment received when taking part?

All treatment you may have in this study can have unwanted side effects and not all side effects are known. When you come for your hospital visit, we will ask you about any side effects you have experienced. It is important that you tell us about any problems, as it is often possible to deal with side effects by adjusting the study treatment or giving you some other medication. We will monitor you closely for any possible side effects and they may suggest additional investigations if appropriate.

If you need to contact us at any time, for example if you become suddenly unwell between hospital visits, please telephone us immediately for advice. When you join the study, we will give you a contact card, which will also let you know the correct number to call. You should carry this with you at all times. If you are admitted to a hospital or have to see your GP in between hospital visits, please remember to show them the contact card in case they need to speak to us.

If you suffer from something that you think may be related to your study treatment or you become concerned about any side effects, please contact us.

Side effects of Standard Radiotherapy or Proton Beam Therapy Treatments:

If you are in the group of patients having standard (IMRT) radiotherapy (group 1), there is the chance that you may experience more side effects than patients having proton beam therapy (group 2). However, we do not know whether this will be the case and one of the aims of this study is to investigate this further.

All types of radiotherapy to the oesophagus may cause:

Possible early or short-term side-effects: Start during radiotherapy or shortly after completing radiotherapy and usually resolve within 1-3 months of finishing radiotherapy. (Frequencies are approximate)

Expected 50-100%

- Tiredness
- Skin soreness, redness and itching in the treatment area
- Increased saliva or mucous production
- Loss of appetite which may lead to weight loss
- Inflammation of the oesophagus which may cause pain and/or difficulty with swallowing
- Indigestion or heartburn
- Nausea or vomiting
- Abdominal discomfort or bloating

Common 10-50%

- Hair loss in treatment area
- Inflammation of the lungs – causing cough or shortness of breath
- Feeding via a tube into the stomach/small intestine
- Admission to hospital for control of side-effects
- Sore mouth or throat

Less common <10%

- Mouth ulcers
- Change in voice

Rare <1%

- Pneumonia
- Risk of an oesophageal fistula – abnormal connection between the oesophagus and airways

Possible late or long-term side-effects: May happen many months or years after radiotherapy and may be permanent. (Frequencies are approximate).

Common 10-50%

- Ongoing fatigue
- Fibrosis (scarring) of the underlying lung which can cause breathlessness, cough or changes on X-ray

Less than common <10%

- Hypothyroidism – a hormone deficiency, this may require you to take medications
- Risk of damage to the heart – risk depends on the position of the tumour in the oesophagus
- Skin changes in the treatment area including: Altered colour usually lighter or darker, scarring, Telangiectasia (small visible blood vessels which look like spidery marks).

Rare <1%

- Oesophageal or gastric ulceration or perforation (tear) which may require surgery

- Oesophageal fistulation – abnormal connection between the oesophagus and airways. Long-term need for feeding via a tube.
- Bleeding which may require endoscopic treatment or surgery
- Myelitis – inflammation of nerves which may cause a change in muscle power or sensation
- Risk of rib/vertebral fracture
- Hyposplenism – the spleen no longer functions which lowers immunity and may require additional vaccinations and prophylactic antibiotics
- Long-term decline in kidney function
- A different cancer in the treatment area
- Death

Side effects of chemotherapy, surgery and immunotherapy (standard of care):

Your hospital doctor will explain the possible side effects of the chemotherapy, surgery and immunotherapy with you as these are all standard of care.

Are there any other risks of this study?

If you take part in this study you will have PET/CT imaging scans, MUGA and radiotherapy treatment. These procedures use ionising radiation to form images of your body, provide your doctor with other clinical information and provide treatment. Ionising radiation may cause cancer many years or decades after the exposure. In patients with your current clinical condition, the chance of this happening to you is extremely small.

Summary:

- We do not know what side affects you will have. There are many possible side effects listed above.
- You can contact your hospital doctor/study team at any time if you are worried or develop any of the symptoms of the side effects.
- If the side effects are too severe, you may have to stop taking part in the study.
- Carry your PROTIEUS study contact card with you at all times.

11. Pregnancy and Contraception

Please share this information with your partner if appropriate.

For women:

- Chemotherapy, radiotherapy, and immunotherapy are known to be harmful to unborn babies and chemotherapy and immunotherapy may be present in breast milk. Therefore, if you are pregnant or breast-feeding you will not be able to take part in the study.

- If there is a chance that you could become pregnant, we will ask you to take a pregnancy test (urine or blood) before entering the study to ensure you are not pregnant.
- You must agree to use contraception during your treatment. This must continue for the time you are receiving treatment and for up to 6 months after you finish your last chemotherapy or immunotherapy treatment.
- If you do become unexpectedly pregnant during the study, you must inform us immediately. We would discuss referral for specialist counselling on the possible risks to yourself and your unborn baby.
- Patients who become pregnant whilst on the study may need to stop treatment immediately.

For men:

- Please share this information with your partner if there is a possibility that your partner is pregnant or that they might become pregnant.
- Chemotherapy and radiotherapy may affect sperm or semen and therefore you should not expose an unborn child to the sperm during the study and for up to 6 months after you finish your chemotherapy and radiotherapy treatment.
- You must use barrier contraception during sexual intercourse if your partner might become pregnant or is already pregnant. If your partner might become pregnant, you must advise them to use contraception during your treatment and for up to 6 months afterwards.
- If your partner becomes pregnant during the study, or within 6 months of you stopping treatment, you must tell us immediately.
- If your partner is already pregnant and you did not use barrier contraception while on treatment, you must tell us immediately.
- We would discuss referral for specialist counselling on the possible risks to your partner and your unborn baby.

Fertility Advice:

Due to the possibility of treatment-related infertility, we will provide you with information on egg cryo-preservation or sperm banking. Please let us know if you would like to discuss this further and if you would like further information.

12. What happens when the study stops?

You will be seen in your local hospital every 3-6 months for another 2-3 years and will be checked with scans at regular intervals.

13. What are the alternatives for treatment?

If for some reason the tests show you should not take part in the study your hospital doctor will discuss with you any available alternative treatment options that may be suitable for you.

Standard treatment options for oesophageal cancer include:

- Chemotherapy and immunotherapy and radiotherapy before surgery, followed by immunotherapy
- Chemotherapy before surgery, followed by more chemotherapy and immunotherapy
- Chemotherapy followed by chemotherapy and radiotherapy
- Surgery alone

14. Do I have to take part?

No. It is up to you to decide whether or not you would like to take part in the study. We will describe what would be involved and go through this Patient Information Sheet with you. This Patient Information Sheet is yours to take away so that you have the opportunity to read it carefully and discuss it with others if you wish. If you decide to take part, we will ask you to sign a consent form of which you will be given a copy. You are free to withdraw at any time, without giving a reason.

If you decide not to take part, or later to withdraw, this will not affect the care you receive from us in any way. If you choose to stop taking part in the study, we would like to continue collecting information about your health from central NHS records. If you do not want this to happen, tell us and we will stop. Any stored blood or tissue samples that can be identified as yours will be destroyed if you wish.

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 that we hold about you.

If you decide not to take part in this research study, you may be asked if you would like to take part in the observational study for PROTIEUS, and we will discuss this with you.

15. More information about taking part

Support for patients receiving Proton Beam Therapy:

If you are allocated to proton beam therapy (group 2), you will need to visit one of the two national NHS proton centres for treatment planning and the treatment itself. The proton centres are located at the Christie NHS Foundation Trust in Manchester and the University College Hospital in London. Following your confirmation that you wish to take part in the study you will be contacted by a 'key worker', a named specialist nurse or radiographer, from one of the proton centres, who will help and support you throughout your treatment. Your key worker at the proton centre will call you to discuss travel and accommodation during

treatment and to answer any questions you have before you arrive at the hospital. Please read all the information you have received from your local hospital before this phone call, so that they can best answer your questions.

Accommodation during Proton Beam Therapy:

If you do not live near the NHS proton therapy centre, arrangements for free accommodation will be made by the key worker from the proton centre. This would be for you plus one family member or carer for your planning visit, and for the whole of your 3 weeks of proton beam treatment. The types of accommodation available will vary to accommodate your specific needs. You do not have to stay in the provided accommodation if you live close to the NHS proton centre and would prefer to return home every day following your treatment.

Only accommodation approved by the NHS proton centre will be funded by the NHS. Further details about the accommodation provided will be provided by your key worker.

Once you have received your visit schedule from the key worker at the proton centre, you will need to make your own travel arrangements.

If you are in group 2 (Proton beam therapy) you may be eligible for help from the NHS Travel costs scheme: https://www.nhs.uk/NHSEngland/Healthcosts/Pages/Travelcosts.aspx

In addition, Macmillan provide information to help with travel expenses:

https://www.macmillan.org.uk/information-and-support/organising/benefits-and-financial-support/help-with-transport-and-parking/travel-parking-hospital.html

16. How will we use information about you?

University College London (UCL) is the Sponsor and Data Controller for this study and it is run on their behalf by the Cancer Research UK & UCL Cancer Trials Centre (UCL CTC), based in the United Kingdom. UCL CTC will be using information from you and your medical records in order to undertake this study, which means in legal terms, patient data is being used as part of a task in the public interest. This means that UCL CTC are responsible for looking after your information and using it properly. UCL CTC will keep identifiable information about you for at least 5 years after the study has finished.

The information collected will include:

By your hospital doctor or study team:

- Your name, date of birth, NHS number and contact details (including address and/or telephone number).
- Your GP's details.

By UCL (the sponsor for this study based in the United Kingdom) or our representatives:

- Your initials, NHS number, date of birth, postcode and gender (this is to follow your progress once your study visits have finished).
- Your ethnicity and race, however, you can choose not to provide this information if you wish.
- Personal information as well as details of previous treatment, current treatment, previous medical conditions, and medications.
- If you become pregnant, information about you (or your partner), the pregnancy and your baby.
- Your scans, scan reports and surgical photographs.

Laboratories that will be processing, storing and/or analysing your blood and tissue samples as part of this study:

- Your initials and study number.
- The results from the analyses of your sample which will be sent to UCL to use as part of the study results.

The people within the organisations above will use this information to do the research or to check your records to make sure that the research is being done properly. People within the organisations who do not need to know who you are will not be able to see your name or contact details. Your data will have a unique study number instead which we will provide to you when you enroll onto the study. We will keep all information about you safe and secure.

Your initials and study number will be marked on the tissue samples that are collected and sent to the central laboratory. This is to make sure that your samples are not mixed up with those from other patients. The laboratory will make sure your information is held securely and not shared with anyone else.

Your initials and study number will be marked on the scans, scan reports and surgical photographs that are collected and sent to the sponsor. This is to make sure that your images are not mixed up with those from other patients. UCL will make sure your information is held securely and not shared with anyone else.

Your medical notes will need to be seen by authorised individuals from UCL and our representatives, regulatory authorities, and your NHS Trust/Health Board. This is to ensure that the study is being carried out properly and that the information collected is accurate.

We plan to collect information about you to follow your progress after you have had surgery. This information will be collected from the NHS through NHS Digital and be collected for up to 2 years after your surgery. To be able to access these records, we will need to provide them with your date of birth, postcode and NHS number. These details will be used to trace your health records and if there is a match, they will send us information on your health status. You do not need to do anything more for the study. All data shared with these organisations will be handled under strict rules covering data protection and confidentiality, and data sharing contracts will be put in place.

Once we have finished the study, we will keep some of the data 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 if relevant new information becomes available?

Sometimes we get new information about treatments being studied. If this happens, your hospital doctor will tell you and discuss with you whether you should continue in the study. If you decide not to carry on, they will arrange for your care to continue outside the study. If you decide to continue in the study, you will need to sign an updated consent form.

In some circumstances, your hospital doctor might consider it to be in your best interests to withdraw you from the study. If this is the case, your hospital doctor will explain the reasons and arrange for your care to continue outside of the study. If you decide to continue in the study, you may be asked to sign an updated consent form.

If the study is stopped for any other reason, your hospital doctor will tell you and arrange your continuing care.

Will my General Practitioner (GP) be informed that I am taking part in this research study?

We will tell your GP about your participation in the study. We may also contact your GP to obtain information about your health status in some cases, for example if you miss a study visit at the hospital. We will also contact your GP for follow-up data if we cannot get in contact with you.

What are your choices about how your information is used?

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

If you choose to stop taking part, we would like to continue to collect information about you from your hospital doctor, so that we know about your progress following study treatment. If you do not want this to happen, tell your hospital doctor and we will stop.

Any stored blood or tissue samples that can be identified as yours will be destroyed if you wish.

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 that we hold about you.

If you agree to take part in this study, you will have the option to take part in future research using your data and/or blood. Your data and samples will be stored securely and any future research that uses your data or samples will be approved by a Research Ethics Committee before being used.

What would happen if you lost the capacity to make decisions whilst on the study?

If you lost the capacity to make decisions or to communicate your decisions whilst on the study we would withdraw you from the trial and make sure you continued to receive the most appropriate care and treatment.

We would keep all the information already collected about you for the trial and any samples collected for the trial (labelled with your study number and initials). We would stop collecting any further information about you, and we would not collect any more samples from you for the trial.

Where can you find out more about how your information is used?

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

- At www.hra.nhs.uk/information-about-patients
- In the Health Research Authority's Patient Data and Research Leaflet, provided to you along with this information sheet.
- In the UCL General Privacy Notice for Participants and Researchers in Health and Care Research Studies https://www.ucl.ac.uk/legal-services/privacy/ucl-general-privacy-notice-participants-and-researchers-health-and-care-research-studies
- By asking your hospital doctor or one of the research team, or
- By sending an email to data-protection@ucl.ac.uk

What if there is a problem?

Every care will be taken in the course of this study. However, in the unlikely event that you are injured by taking part, compensation may be available.

If you suspect that the injury is the result of the UCL or the hospital's negligence, then you may be able to claim compensation. After discussing with your hospital doctor, please make the claim in writing to Professor Maria Hawkins who is the Chief Investigator for the study and is based at University College London (c/o Cancer Trials, Cancer Research UK & UCL Cancer Trials Centre, 90 Tottenham Court Road, London, W1T 4TJ). The Chief Investigator will then pass the claim to the Sponsor and on to the Sponsor's Insurers. If you have a claim, then it might be helpful to consult a lawyer. Participants may also be able to claim compensation for injury caused by participation in this study without the need to prove negligence on the part of UCL or another party. You should discuss this possibility with your hospital doctor in the same way as above.

Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been approached or treated by members of staff or about any side effects that you may have experienced due to your participation in the study, the normal National Health Service complaints mechanisms are available to you. Please ask your hospital doctor if you would like more information on this. Details can be obtained from the NHS website.

You can also contact PALS (Patient Advice Liaison Service) which offers confidential advice, support and information on health-related matters to patients, their families and carers. Please ask your research nurse for further information if you would like contact details of your local service.

What will happen to the results of the study?

UCL CTC will publish a summary of the results on their website, the Cancer Research UK website, and in medical journals, so that others can see them. Your identity and any personal details will be kept confidential. No named information about you will be published in any report of the study.

Once the results of the study have been published, they will be available to the public on the internet (e.g. hospital websites etc.).

We will have a summary of the results which your hospital doctor can give to you and your family or carers. They would also be happy to explain the results of the study to you and to answer any questions you have.

Who is organising and funding this study?

UCL is the sponsor for this study based in the United Kingdom. The study is being run by Cancer Research UK & UCL Cancer Trials Centre, which is part of University College London. The study is funded by Cancer Research UK and the Taylor Family Foundation charities.

UCL will be using information from you and your medical records in order to undertake this study and will act as the data controller for this study.

This hospital will receive a payment to help cover the costs of this research, however, your hospital doctor will not be paid directly for including you in this study.

How have patients been involved in the study?

When we designed this study, we considered the opinions of patients regarding the way patients will be randomised in the study, the number of visits to the proton centre, the preference to have treatment closer to home and on the information provided in this Patient Information Sheet.

Who has reviewed the study?

All research in the NHS is looked at by an independent group of people, called a Research Ethics Committee, to protect the interests of any patients that may take part. This study has been reviewed and approved by the London - Camden & Kings Cross Research Ethics Committee and has also been approved by the Health Research Authority (HRA).

Thank You:

Thank you so much for considering taking part in this study and for taking the time to read this Patient Information Sheet, which is yours to keep. If you decide to take part in the study, we will also give you a copy of your signed consent form.

Further Information:

You may wish to contact one of the following organisations that are independent of the hospital at which you are being treated:

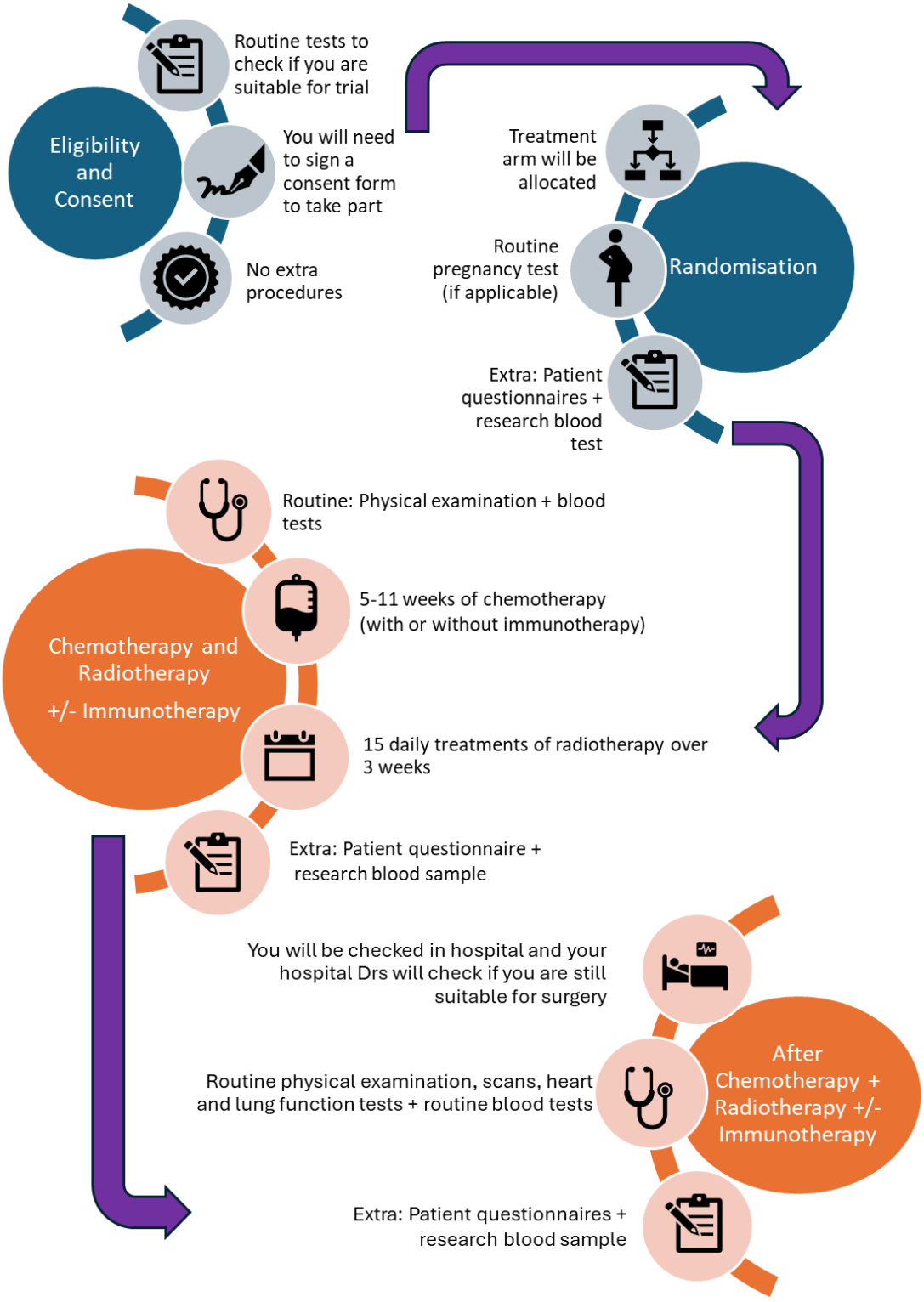
- Macmillan Cancer Support provides practical, medical and financial support and work towards improving cancer care. They can be contacted at:

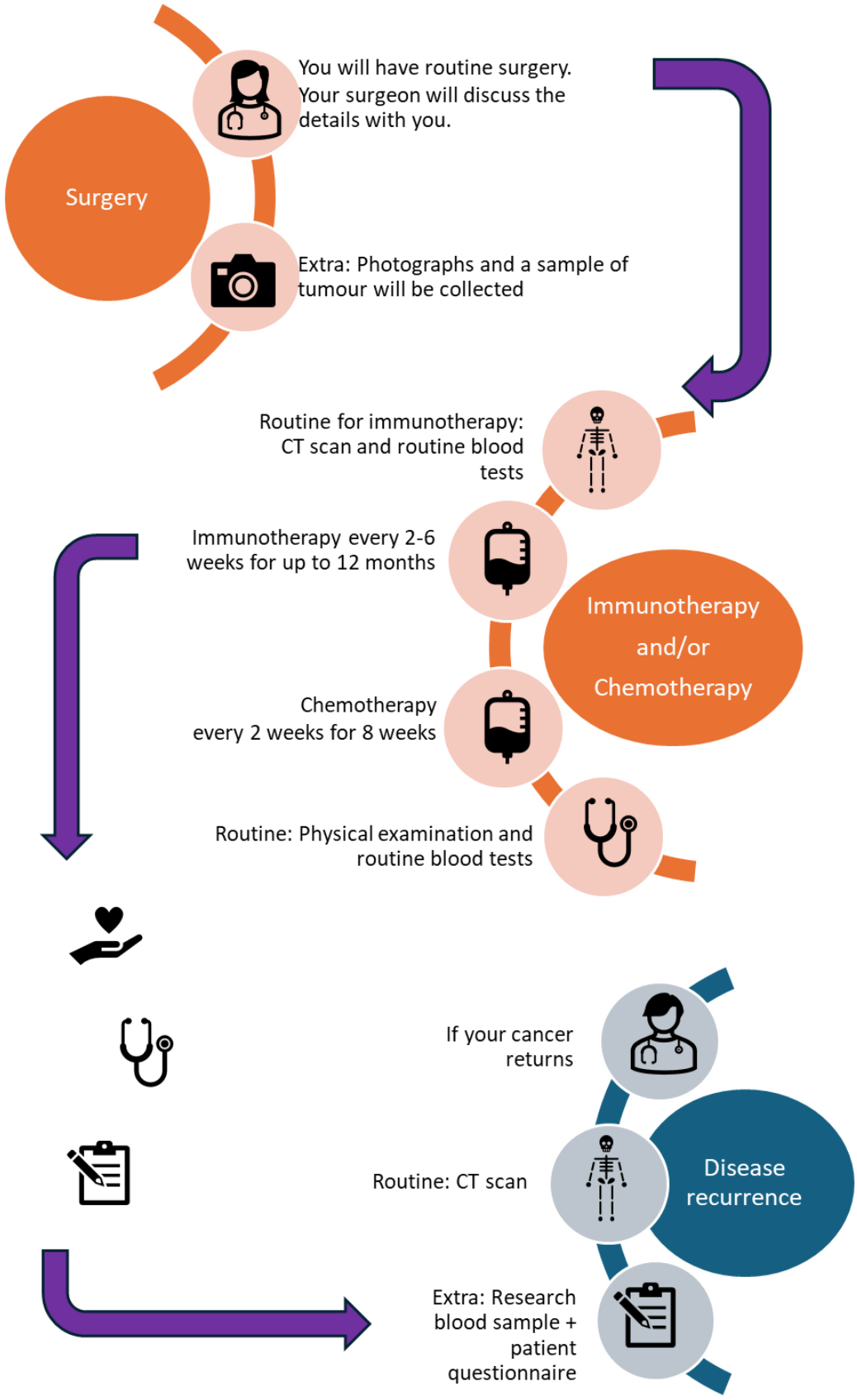
- Tel: 0808 808 00 00 (Freephone)
- Or visit their website at: https://www.macmillan.org.uk/

- About Cancer (Cancer Research UK) who provide all aspects of information for people with cancer. Their contact details are:
  - Tel: 0300 123 1022 (General enquiries), 0808 800 4040 (Cancer-related questions)
  - Or visit their website at: https://www.cancerresearchuk.org/about-cancer

17. Summary of your participation in the PROTIEUS Study:

Here is a summary of the procedures you will have if you take part in the trial, but you will receive a personalised timetable for all your appointments.




Surgery
You will have routine surgery. Your surgeon will discuss the details with you.
Extra: Photographs and a sample of tumour will be collected
Routine for immunotherapy: CT scan and routine blood tests
Immunotherapy every 2-6 weeks for up to 12 months
Immunotherapy and/or Chemotherapy
Chemotherapy every 2 weeks for 8 weeks
Routine: Physical examination and routine blood tests
If your cancer returns
Routine: CT scan
Disease recurrence
Extra: Research blood sample + patient questionnaire