Welcome to the Integrated Research Application System

IRAS Project Filter

The integrated dataset required for your project will be created from the answers you give to the following questions. The system will generate only those questions and sections which (a) apply to your study type and (b) are required by the bodies reviewing your study. Please ensure you answer all the questions before proceeding with your applications.

Please complete the questions in order. If you change the response to a question, please select 'Save' and review all the questions as your change may have affected subsequent questions.

Please enter a short title for this project (maximum 70 characters)
Renal Adjuvant MultiPle Arm Randomised Trial (RAMPART)

1. Is your project research?

(●) Yes ( ) No

2. Select one category from the list below:

(●) Clinical trial of an investigational medicinal product

( ) Clinical investigation or other study of a medical device

( ) Combined trial of an investigational medicinal product and an investigational medical device

( ) Other clinical trial to study a novel intervention or randomised clinical trial to compare interventions in clinical practice

( ) Basic science study involving procedures with human participants

( ) Study administering questionnaires/interviews for quantitative analysis, or using mixed quantitative/qualitative methodology

( ) Study involving qualitative methods only

( ) Study limited to working with human tissue samples (or other human biological samples) and data (specific project only)

( ) Study limited to working with data (specific project only)

( ) Research tissue bank

( ) Research database

If your work does not fit any of these categories, select the option below:

( ) Other study

2a. Is this a commercially sponsored Phase 1 or Phase 1/2a trial involving healthy volunteers?

( ) Yes (●) No

2b. Will the study involve the use of any medical device without a CE Mark, or a CE marked device which has been modified or will be used outside its intended purposes?

( ) Yes (●) No

2c. Please answer the following question:

Is this trial subject to advice from the Expert Advisory Group on Clinical Trials and the Commission on Human Medicine prior to authorisation from MHRA? ○ Yes ◉ No

2d. Please answer the following question:

Is this a trial of a gene therapy medicinal product? ○ Yes ◉ No

2e. Please answer the following question(s):

a) Does the study involve the use of any ionising radiation? ◉ Yes ○ No

• Does the study involve exposure to radioactive materials? ○ Yes ◉ No

b) Will you be taking new human tissue samples (or other human biological samples)? ◉ Yes ○ No

c) Will you be using existing human tissue samples (or other human biological samples)? ◉ Yes ○ No

3. In which countries of the UK will the research sites be located?*(Tick all that apply)*

- ☑ England
- ☑ Scotland
- ☑ Wales
- ☑ Northern Ireland

3a. In which country of the UK will the lead NHS R&D office be located:

- ◉ England
- ○ Scotland
- ○ Wales
- ○ Northern Ireland
- ○ This study does not involve the NHS

4. Which applications do you require?

IMPORTANT: If your project is taking place in the NHS and is led from England select 'IRAS Form'. If your project is led from Northern Ireland, Scotland or Wales select 'NHS/HSC Research and Development Offices' and/or relevant Research Ethics Committee applications, as appropriate.

- ☑ IRAS Form
- ☑ Medicines and Healthcare products Regulatory Agency (MHRA) – Medicines
- ☐ Confidentiality Advisory Group (CAG)
- ☐ National Offender Management Service (NOMS) (Prisons & Probation)

For NHS/HSC R&D Offices in Northern Ireland, Scotland and Wales the CI must create NHS/HSC Site Specific Information forms, for each site, in addition to the study wide forms, and transfer them to the PIs or local collaborators.

For participating NHS organisations in England different arrangements apply for the provision of site specific information. Refer to IRAS Help for more information.

5. Will any research sites in this study be NHS organisations?

◉ Yes ○ No

5a. Are all the research costs and infrastructure costs (funding for the support and facilities needed to carry out research e.g. NHS Support costs) for this study provided by a NIHR Biomedical Research Centre, NIHR Biomedical Research Unit, NIHR Collaboration for Leadership in Health Research and Care (CLAHRC), NIHR Patient Safety Translational Research Centre or a Diagnostic Evidence Co-operative in all study sites?

Please see information button for further details.

○ Yes ◉ No

Please see information button for further details.

5b. Do you wish to make an application for the study to be considered for NIHR Clinical Research Network (CRN) Support and inclusion in the NIHR Clinical Research Network Portfolio?

Please see information button for further details.

◉ Yes ○ No

The NIHR Clinical Research Network provides researchers with the practical support they need to make clinical studies happen in the NHS e.g. by providing access to the people and facilities needed to carry out research "on the ground".

If you select yes to this question, you must complete a NIHR Clinical Research Network (CRN) Portfolio Application Form (PAF) immediately after completing this project filter question and before submitting other applications. Failing to complete the PAF ahead of other applications e.g. HRA Approval, may mean that you will be unable to access NIHR CRN Support for your study.

6. Do you plan to include any participants who are children?

○ Yes ◉ No

7. Do you plan at any stage of the project to undertake intrusive research involving adults lacking capacity to consent for themselves?

○ Yes ◉ No

Answer Yes if you plan to recruit living participants aged 16 or over who lack capacity, or to retain them in the study following loss of capacity. Intrusive research means any research with the living requiring consent in law. This includes use of identifiable tissue samples or personal information, except where application is being made to the Confidentiality Advisory Group to set aside the common law duty of confidentiality in England and Wales. Please consult the guidance notes for further information on the legal frameworks for research involving adults lacking capacity in the UK.

8. Do you plan to include any participants who are prisoners or young offenders in the custody of HM Prison Service or who are offenders supervised by the probation service in England or Wales?

○ Yes ◉ No

9. Is the study or any part of it being undertaken as an educational project?

○ Yes ◉ No

10. Will this research be financially supported by the United States Department of Health and Human Services or any of its divisions, agencies or programs?

○ Yes ◉ No

11. Will identifiable patient data be accessed outside the care team without prior consent at any stage of the project (including identification of potential participants)?

○ Yes ◉ No

Integrated Research Application System
Application Form for Clinical trial of an investigational medicinal product

IRAS Form (project information)

Please refer to the E-Submission and Checklist tabs for instructions on submitting this application.

The Chief Investigator should complete this form. Guidance on the questions is available wherever you see this symbol displayed. We recommend reading the guidance first. The complete guidance and a glossary are available by selecting Help.

Please define any terms or acronyms that might not be familar to lay reviewers of the application.

Short title and version number: (maximum 70 characters - this will be inserted as header on all forms)
Renal Adjuvant MultiPle Arm Randomised Trial (RAMPART)

Please complete these details after you have booked the REC application for review.

REC Name:
London-Riverside

REC Reference Number:
17/LO/1875

Submission date:
06/11/2017

PART A: Core study information

1. ADMINISTRATIVE DETAILS

A1. Full title of the research:

Renal Adjuvant MultiPle Arm Randomised Trial (RAMPART): An international investigator-led phase III multi-arm multi-stage randomised controlled platform trial of adjuvant therapy in patients with resected primary renal cell carcinoma (RCC) at high or intermediate risk of relapse

A3-2. National coordinating investigator (for a multicentre trial) **or principal investigator** (for a single centre trial)

- (●) National coordinating investigator
- ( ) Principal investigator

Given name	James
Family name	Larkin
Qualification (MD...)	FRCP PhD GMC Registration: Full (No. 4320007)
ORCID ID	
Institution name	Royal Marsden Hospital
Institution department name	Sycamore House
Street address	Downs Road
Town/city	Sutton

Post Code	SM2 5PT
Country	UNITED KINGDOM
Work E-mail	james.larkin@rmh.nhs.uk
* Personal E-mail	james.larkin@rmh.nhs.uk
Work Telephone	02086613979
* Personal Telephone/Mobile	
Fax	02086613541

** This information is optional. It will not be placed in the public domain or disclosed to any other third party without prior consent.*
A copy of a current CV (maximum 2 pages of A4) for the Chief Investigator must be submitted with the application.

A4. Who is the contact on behalf of the sponsor for all correspondence relating to applications for this project?
This contact will receive copies of all correspondence from REC and HRA/R&D reviewers that is sent to the CI.

	Title	Forename/Initials	Surname
		RAMPART	Trial Management Team
Address	MRC Clinical Trials Unit at UCL		
	90 High Holborn		
Post Code	WC1V 6LJ		
E-mail	mrcctu.rampart@ucl.ac.uk		
Telephone	02076704683/4743		
Fax	020 76704818		

A5-1. Research reference numbers. *Please give any relevant references for your study:*

Applicant's/organisation's own reference number, e.g. R & D (if available):	
Sponsor's/protocol number:	RE06
Protocol Version:	1.0
Protocol Date:	03/10/2017
Funder's reference number:	KCUK 0004
Project website:	https://www.rampart-trial.org/

Registry reference number(s):
The Department of Health's Research Governance Framework for Health and Social Care and the research governance frameworks for Wales, Scotland and Northern Ireland set out the requirement for registration of trials. Furthermore: Article 19 of the World Medical Association Declaration of Helsinki adopted in 2008 states that "every clinical trial must be registered on a publicly accessible database before recruitment of the first subject"; and the International Committee of Medical Journal Editors (ICMJE) will consider a clinical trial for publication only if it has been registered in an appropriate registry. Please see guidance for more information.

International Standard Randomised Controlled Trial Number (ISRCTN):	ISRCTN53348826
ClinicalTrials.gov Identifier (NCT number):	NCT03288532
European Clinical Trials Database (EudraCT) number:	2017-002329-39

Additional reference number(s):

Ref.Number Description	Reference Number

A5-2. Is this application linked to a previous study or another current application?

◯ Yes ◉ No

Please give brief details and reference numbers.

2. OVERVIEW OF THE RESEARCH

To provide all the information required by review bodies and research information systems, we ask a number of specific questions. This section invites you to give an overview using language comprehensible to lay reviewers and members of the public. Please read the guidance notes for advice on this section.

A6-1. Summary of the study. *Please provide a brief summary of the research (maximum 300 words) using language easily understood by lay reviewers and members of the public. Where the research is reviewed by a REC within the UK Health Departments' Research Ethics Service, this summary will be published on the Health Research Authority (HRA) website following the ethical review. Please refer to the question specific guidance for this question.*

Renal cell carcinoma is a type of kidney cancer that starts from the kidneys. It is the 8th most common cancer in the UK and an increase of new cases of 2% has been seen in the last twenty years. About half of the new cases of kidney cancer are among people aged 70 and above.

Patients whose disease has not spread outside the kidneys typically have surgery to remove a part or all of their kidney (called a partial or radical nephrectomy). After surgery, patients are seen by their doctor with regular check-ups to look for signs of the cancer coming back or spreading to other parts of the body; this is generally called 'active monitoring' or 'active surveillance'. Unfortunately, it is estimated that the cancer will return in 30-40% of the patients who have undergone surgery.

Many clinical studies have been carried out to find if a new treatment after surgery might slow the cancer coming back or prevent it from coming back altogether. However, to date no treatment is available. Immunotherapy is a type of cancer treatment that 'wakes up' the patient's own immune system so it can fight the cancer. New drugs which act in this way have worked well in patients with skin cancer (melanoma), lung cancer and in patients with kidney cancer that has spread outside the kidney.

RAMPART is a study looking at two new immunotherapy treatments. We aim to find out whether taking one drug (durvalumab) or a combination of two drugs (durvalumab and tremelimumab) for one year can prevent or delay kidney cancer from coming back compared to the current standard of care (active monitoring after surgery).

Durvalumab is sometimes referred to as an anti-PDL1 drug, and it is currently being tested (alone or in combination with other drugs) in many types of cancer. Tremelimumab is sometimes called anti-CTLA4 drug. It is also being tested in different types of cancer. Like all drugs, these treatments have side effects and patients will have regular blood tests, scans and appointments with their study doctor and nurse.

Around 1,750 patients from the UK, Australia, France and the US will join the study. It will take approximately 5.5 years to reach this number. The first results from the study are expected 6.5 years after the study starts, with more results following later. If positive, the results of the study will change the current standard of care for the treatment of kidney cancer after surgery.

A6-2. Summary of main issues. *Please summarise the main ethical, legal, or management issues arising from your study and say how you have addressed them.*

Not all studies raise significant issues. Some studies may have straightforward ethical or other issues that can be identified and managed routinely. Others may present significant issues requiring further consideration by a REC, HRA, or other review body (as appropriate to the issue). Studies that present a minimal risk to participants may raise complex organisational or legal issues. You should try to consider all the types of issues that the different reviewers may need to consider.

No significant ethical, legal or management issues are expected to arise from the study; however both experimental treatments have never been used in the adjuvant kidney cancer setting before. Therefore, close monitoring of side effects will be required for patients randomised to the experimental research arms. An early safety analysis has been built into the trial design and is planned to take place either once 70 patients have been randomised into the trial (and completed at least 1 treatment cycle) or 6 months after starting the trial (whichever is earliest).

3. PURPOSE AND DESIGN OF THE RESEARCH

A7. Select the appropriate methodology description for this research. *Please tick all that apply*:

- ☐ Case series/ case note review
- ☐ Case control
- ☐ Cohort observation
- ☐ Controlled trial without randomisation
- ☐ Cross-sectional study
- ☐ Database analysis
- ☐ Epidemiology
- ☐ Feasibility/ pilot study
- ☐ Laboratory study
- ☐ Metanalysis
- ☐ Qualitative research
- ☐ Questionnaire, interview or observation study
- ☑ Randomised controlled trial
- ☐ Other (please specify)

A8. Type of medicinal trial:

- ☑ Clinical trial of an unlicensed investigational medicinal product
- ☐ Clinical trial of a licensed medicinal product in new conditions of use (different from those in the SmPC, i.e. new target population, new dosage schemes, new administration route, etc.)
- ☐ Clinical trial of a licensed medicinal product used according to the SmPC
- ☐ Other (please specify)

A9. Phase of medicinal trial: *(Tick one category only)*

Human pharmacology (Phase I)	○ Yes	◉ No
Therapeutic exploratory trial (Phase II)	○ Yes	◉ No
Therapeutic confirmatory trial (Phase III)	◉ Yes	○ No
Therapeutic use trial (Phase IV)	○ Yes	◉ No

A10. What is the principal research question/objective? *Please put this in language comprehensible to a lay person.*

The RAMPART trial is aiming to address two research questions:

1. Does treatment with either durvalumab alone or a combination of durvalumab and tremelimumab delay the cancer from coming back compared with the current standard-of-care (active monitoring) in patients with kidney cancer who underwent surgery and are at intermediate or high risk of recurrence?

2. Does treatment with either durvalumab alone or a combination of durvalumab and tremelimumab increase life expectancy compared with current standard-of-care (active monitoring) in patients with kidney cancer who underwent surgery and are at intermediate or high risk of recurrence?

A11. What are the secondary research questions/objectives if applicable? *Please put this in language comprehensible to a lay person.*

There are a number of secondary research questions that the RAMPART trial is aiming to address:

1. Does treatment with either durvalumab alone or a combination of durvalumab and tremelimumab delay the cancer from spreading outside the kidneys?

2. Does treatment with either durvalumab alone or a combination of durvalumab and tremelimumab reduces the chances of dying from kidney cancer?

3. How does treatment with either durvalumab alone or a combination of durvalumab and tremelimumab affect the quality of life of patients?

4. What side effects are experienced in patients undergoing treatment with either durvalumab alone or a combination of durvalumab and tremelimumab?

5. What are patients' preferences when it comes to treatments affecting the immune system?

A12. What is the scientific justification for the research? *Please put this in language comprehensible to a lay person.*

The current standard-of-care worldwide, for patients with kidney cancer that have undergone surgery and whose cancer has not spread outside the pelvis, is active monitoring by the clinical team through regular CT scans. Unfortunately, the disease is estimated to spread outside the kidneys in 30-40% patients who have undergone surgery.

So far no treatment has been shown to delay kidney cancer from coming back or extend life expectancy. The need for new treatments is particularly important in those patients with a high risk of recurrence whose life expectancy can be particularly poor.

Finding an effective treatment or combination of treatments that can prevent the disease from coming back, or at least delay its return, would be hugely beneficial for the current standard-of-care and would contribute to the national and worldwide cancer strategy.

A13. Please summarise your design and methodology. *It should be clear exactly what will happen to the research participant, how many times and in what order. Please complete this section in language comprehensible to the lay person. Do not simply reproduce or refer to the protocol. Further guidance is available in the guidance notes.*

The RAMPART trial uses a novel design called Multi-Arm Multi-Stage (MAMS) design. This type of statistical design allows several treatments (or combinations of treatments) to be tested at the same time. The design also offers the possibility to review the accumulated data at pre-defined points to gauge whether any benefit or harm is being done to the patients. This can then inform decisions on whether to stop early or continue with trial recruitment.

At the start of recruitment patients with Leibovich score 3-11 will be eligible for randomisation. We will monitor accrual and stop recruiting intermediate risk patients (Leibovich Score 3-5) after three years or when intermediate risk patients contribute 25% of the total accrual target, whichever is earlier. Recruitment of patients with Leibovich Score 6-11 will continue until the final accrual target is reached (approximately 1750 patients).

Patients will be randomly assigned according to a 3:2:2 ratio to one of the following trial arms:

- Arm A (approx. 750 patients): Active monitoring for 1 year
- Arm B (approx. 500 patients): Durvalumab (1500mg) 4 weekly for 1 year (13 cycles)
- Arm C (approx. 500 patients): Durvalumab (administered as per arm B, i.e. 13 cycles) and tremelimumab (75mg) on day 1 and week 4 visits (i.e. 2 cycles).

The study hypotheses are:

1. Durvalumab is able to prevent tumour relapse by the inhibition of the programmed cell death 1/programmed death ligand 1 pathway, which plays a critical role in tumour immune evasion.

2. Combination treatment with anti-CTLA4 agent tremelimumab increases immune response and anti-tumour activity.

Two primary outcome measures will be assessed in this study:

1. Disease Free Survival (DFS), defined as the time from randomisation to the first recurrence of local disease, new primary kidney cancer, metastasis outside the abdominal kidney area or death by any cause

2. Overall Survival (OS), defined as the time from randomisation to death by any cause

In depth discussion was undertaken with the Food and Drug Administration (FDA) and European Medicines Agency (EMA) for the choice of DFS as it is less subject to clinician bias than progression-free survival (which is dependent on measurement of growth in lesions already present). The RAMPART trial will have a more frequent computed tomography (CT) scanning schedule in the first 2 years after randomisation compared to other studies in similar settings (ASSURE and SORCE); therefore this approach will minimise the risk of detection bias in relation to the treatment assignment through after a year post-treatment. Electronic copies of patients' imaging scans will be prospectively collected and stored in a secure central repository to enable independent outcome review, blinded to treatment assignment, should the need arise.

A number of pre-planned interim analyses will also be carried out in line with the trial's design to monitor for safety, overwhelming benefit or lack-of-benefit of the experimental treatments being investigated.

After careful consideration by the Trial Development Group (TDG) and consultation with the FDA and EMA, the proposed control arm for the trial will be active monitoring. Active monitoring is the current global standard-of-care after surgery for localised kidney cancer, and as the agents being investigated in RAMPART are administered via infusion, the decision to not use a placebo control will minimise the burden to both patients and the healthcare system.

Patients will be followed-up in outpatient clinics at accredited RAMPART centres across the UK. Where appropriate patients may be followed up via telephone consultation. Follow-up will be performed at regular intervals from the time of randomisation until the trial data matures and results are disseminated to the wider public and scientific community.

During the first year, patients on arm A (active monitoring) will only be assessed at day 1, then at weeks 16, 32 and 52 for their CT scans.

Patients who are allocated to arms B (durvalumab alone) and C (durvalumab and tremelimumab) will need to have more frequent assessments. They will be assessed at day 1, then on a 2 weekly basis until week 8, and then every 4 weeks until the end of year 1.

After year 1, all patients (arms A, B and C) will have the same follow-up schedule. They will be assessed 3 monthly up to year 3, 6-monthly up to year 5 and annually thereafter.

Additional assessments may be conducted as clinically required the local investigator. A full follow-up schedule is available in the study protocol and Patient Information Sheet (PIS).

A14-1. In which aspects of the research process have you actively involved, or will you involve, patients, service users, and/or their carers, or members of the public?

- [x] Design of the research
- [x] Management of the research
- [x] Undertaking the research
- [ ] Analysis of results
- [x] Dissemination of findings
- [ ] None of the above

Give details of involvement, or if none please justify the absence of involvement.
The RAMPART Trial Development Group (TDG) is committed to engage with the public and involve patient representatives throughout the development and conduct of the trial.

The RAMPART trial has undergone scientific peer-review by Kidney Cancer UK which supports and endorses patient engagement in all parts of clinical research. Furthermore, two patient representatives have been part of the TDG throughout the initial funding and scientific peer-review process was initiated and have been involved with the development and review of the protocol, Patient Information Sheet and Consent Form.

Both patient representatives will form part of the Trial Management Group, will be invited to attend all meetings and

will be actively involved in discussions focusing on the progress and conduct of the trial, including discussion of the recommendations from the Independent Data Monitoring Committee (IDMC) following the pre-planned interim analyses of the trial data.

In due course, the dissemination of the primary results will be carried out with active engagement of patient groups such as CRUK and KCUK.

More information on the trial Patient and Public Involvement (PPI) activities are detailed in Section 14 of the study protocol.

4. RISKS AND ETHICAL ISSUES

RESEARCH PARTICIPANTS

A15. What is the sample group or cohort to be studied in this research?

Select all that apply:

- [ ] Blood
- [x] Cancer
- [ ] Cardiovascular
- [ ] Congenital Disorders
- [ ] Dementias and Neurodegenerative Diseases
- [ ] Diabetes
- [ ] Ear
- [ ] Eye
- [ ] Generic Health Relevance
- [ ] Infection
- [ ] Inflammatory and Immune System
- [ ] Injuries and Accidents
- [ ] Mental Health
- [ ] Metabolic and Endocrine
- [ ] Musculoskeletal
- [ ] Neurological
- [ ] Oral and Gastrointestinal
- [ ] Paediatrics
- [x] Renal and Urogenital
- [ ] Reproductive Health and Childbirth
- [ ] Respiratory
- [ ] Skin
- [ ] Stroke

Gender:	Male and female participants
Lower age limit: 18	Years
Upper age limit:	No upper age limit

A17-1. Please list the principal inclusion criteria (list the most important, max 5000 characters).

1.Histologically proven RCC (all cell types of RCC are eligible, except for pure oncocytoma, collecting duct, medullary and transitional cell cancer [TCC]); no evidence of residual macroscopic disease on post-operative CT scan after resection of RCC. Patients with treated bilateral synchronous RCCs are eligible.
2.At the start of recruitment patients with Leibovich score 3-11 will be eligible for randomisation. MRC CTU will monitor accrual and stop recruiting intermediate risk patients (Leibovich Score 3-5) after three years or when intermediate risk patients contribute 25% of the total accrual target, whichever is earlier. Recruitment of patients with Leibovich Score 6 11 will continue until the accrual target is reached.
3.Patients should have had surgery at least 28 days but no more than 91 days prior to randomisation date.
4. Post-operative scans should be performed within 28 days prior to randomisation
5.WHO Performance Status 0 or 1.
6.Patient has archival FFPE pathology tissue available, and agrees to provide at least one sample (FFPE tumour block from nephrectomy, or a minimum of 10 unstained slides), as well as a baseline EDTA blood sample for future translational research
7.Adequate normal organ and marrow function
a.Haemoglobin ≥9.0g/dL (transfusions will be allowed within 2 weeks of randomisation in order to achieve the entry criteria).
b.Absolute neutrophil count (ANC) ≥1.5 x 109/L (≥1500 per mm3).
c.Platelet count ≥100 x 109 (≥100,000 per mm3).
d.Bilirubin ≤1.5 x ULN (This will not apply to subjects with confirmed Gilbert's syndrome (i.e., persistent or recurrent hyperbilirubinemia that is predominantly unconjugated in the absence of haemolysis or hepatic pathology), who will be allowed only in consultation with their physician).
e.AST/ALT ≤2.5 x ULN.
f.Calculated Creatinine Clearance level >40mL/min by Cockcroft Gault formula
8.12-lead ECG on which QTcF must be <470 ms. In case of clinically significant ECG abnormalities, including a QTcF value ≥470 ms, two additional 12-lead ECGs should be obtained over a brief period (e.g., 30 minutes) to confirm the finding.
9. Patient must weight ≥30Kg at the time of randomisation
10.Subjects must be ≥ 18 years in age.
11.Written Informed Consent obtained from the patient
12.Both men and women enrolled in this trial must use adequate contraception during the treatment phase of the study and for 6 months afterwards. Egg donation, sperm donation and breastfeeding must be avoided.
13. Evidence of post-menopausal status or negative urinary or serum pregnancy test for female pre menopausal patients. Women will be considered post-menopausal if they have been amenorrhoeic for 12 months without an alternative medical cause. The following age specific requirements apply:
a. Women <50 years of age will be considered post-menopausal if they have been amenorrhoeic for 12 months or more following cessation of exogenous hormonal treatments and if they have luteinising hormone and follicle-stimulating hormone levels in the post-menopausal range for the institution or underwent surgical sterilisation (bilateral oophorectomy or hysterectomy).
b. Women ≥50 years of age will be considered post-menopausal if they have been amenorrhoeic for 12 months or more following cessation of all exogenous hormonal treatments, had radiation-induced menopause with last menses >1 year ago, had chemotherapy induced menopause with last menses >1 year ago, or underwent surgical sterilisation (bilateral oophorectomy, bilateral salpingectomy, or hysterectomy).

A17-2. Please list the principal exclusion criteria (list the most important, max 5000 characters).

1.Previous diagnosis of RCC.
2.Metastatic or macroscopic residual disease.
3.Patients with a single pulmonary nodule ≥5mm diameter are not eligible unless the nodule has had a definite benign diagnosis. Patients with multiple small, less than 5 mm nodules may be eligible if nodules have been shown to be radiologically stable for at least 8 weeks.
4.Prior anticancer treatment (other than nephrectomy) for RCC.
5. Any unresolved toxicity NCI CTCAE Grade ≥2 from previous anticancer therapy with the exception of alopecia, vitiligo, and the laboratory values defined in the inclusion criteria
a. Patients with Grade ≥2 neuropathy will be evaluated on a case-by-case basis after consultation with the Study Physician.
b. Patients with irreversible toxicity not reasonably expected to be exacerbated by treatment with durvalumab or tremelimumab may be included only after consultation with the Study Physician.
6. History of another primary malignancy except for:
a) Malignancy treated with curative intent and with no known active disease ≥5 years before the first dose of IP and of low potential risk for recurrence.
b) Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease.
c) Adequately treated carcinoma in situ without evidence of disease.
7. History of leptomeningeal carcinomatosis.

8. Concurrent enrolment in another clinical study, unless it is an observational (non interventional) clinical study or during the follow up period of an interventional study.
9. Major surgical procedure (as defined by the Investigator) within 28 days prior to the start of treatment. Local surgery of isolated lesions for palliative intent is acceptable.
10. Current or prior use of immunosuppressive medication within 14 days before the first dose of durvalumab or tremelimumab, with the exceptions of intranasal and inhaled corticosteroids or systemic corticosteroids at physiological doses, which are not to exceed 10 mg/day of prednisone, or an equivalent corticosteroid.
11. Active or prior documented autoimmune or inflammatory disorders (including inflammatory bowel disease [e.g., colitis or Crohn's disease], diverticulitis [with the exception of diverticulosis], systemic lupus erythematosus, Sarcoidosis syndrome, or Wegener syndrome [granulomatosis with polyangiitis, Graves' disease, rheumatoid arthritis, hypophysitis, uveitis, etc]). The following are exceptions to this criterion:
a. Patients with vitiligo or alopecia
b. Patients with hypothyroidism (e.g., following Hashimoto syndrome) stable on hormone replacement
c. Any chronic skin condition that does not require systemic therapy
d. Patients without active disease in the last 5 years may be included but only after consultation with the RAMPART Trial Management Team
e. Patients with coeliac disease controlled by diet alone
12. A history of immunodeficiency syndrome. Please consult the MRC CTU at UCL on an individual basis if there is any uncertainty.
13. History of allogeneic organ transplant.
14. Uncontrolled intercurrent illness including, but not limited to:
a. Ongoing or active infection
b. Symptomatic congestive heart failure
c. Uncontrolled hypertension
d. Unstable angina pectoris
e. Uncontrolled cardiac arrhythmia
f. Active peptic ulcer disease or gastritis
g. Active bleeding diatheses
h. Psychiatric illness or social situations that would limit compliance with study requirements or compromise the ability of the subject to give written informed consent.
15.Active infection including
a. Tuberculosis (clinical evaluation that includes clinical history, physical examination and radiographic findings, and TB testing in line with local practice)
b. Hepatitis B (known positive HBV surface antigen (HBsAg) result)
c. Hepatitis C
d. Human immunodeficiency virus (positive HIV 1/2 antibodies). Patients with a past or resolved HBV infection (defined as the presence of hepatitis B core antibody [anti HBc] and absence of HBsAg) are eligible.
Note: Patients positive for hepatitis C (HCV) antibody are eligible only if polymerase chain reaction is negative for HCV RNA.
16. Receipt of live attenuated vaccine within 30 days prior to the start of treatment. Note: Patients, if enrolled, should not receive live vaccine while receiving investigational medicinal product and up to 30 days after the last dose of investigational medicinal product.
17. Pregnant or breastfeeding patients.
18. Any condition that, in the opinion of the investigator, would interfere with evaluation of study treatment or interpretation of patient safety or study results.
19. Known allergy or hypersensitivity to durvalumab or tremelimumab, or any of their excipients.
20. Previous investigational medicinal product assignment in the present study.

RESEARCH PROCEDURES, RISKS AND BENEFITS

A18. Give details of all non-clinical intervention(s) or procedure(s) that will be received by participants as part of the research protocol. *These include seeking consent, interviews, non-clinical observations and use of questionnaires.*

Please complete the columns for each intervention/procedure as follows:

1. Total number of interventions/procedures to be received by each participant as part of the research protocol.
2. If this intervention/procedure would be routinely given to participants as part of their care outside the research, how many of the total would be routine?
3. Average time taken per intervention/procedure (minutes, hours or days)
4. Details of who will conduct the intervention/procedure, and where it will take place.

Intervention or procedure	1	2	3	4

Informed Consent	1	1	15	Outpatient clinic Delegated investigator
Quality of Life Questionnaire (EORTC QLQ-30)	4	0	30	Questionnaire to be completed in Outpatient clinics during routine trial visits
Health Economics Questionnaire (EORTC EQ-5D)	4	0	30	Questionnaire to be completed in Outpatient clinics during routine trial visits
Preference for Adjuvant Immunotherapy in RAMPART (PAIR) Questionnaire	3	0	30	Questionnaire to be completed in Outpatient clinics during routine trial visits

A19. Give details of any clinical intervention(s) or procedure(s) to be received by participants as part of the research protocol. *These include uses of medicinal products or devices, other medical treatments or assessments, mental health interventions, imaging investigations and taking samples of human biological material. Include procedures which might be received as routine clinical care outside of the research.*

Please complete the columns for each intervention/procedure as follows:

1. Total number of interventions/procedures to be received by each participant as part of the research protocol.
2. If this intervention/procedure would be routinely given to participants as part of their care outside the research, how many of the total would be routine?
3. Average time taken per intervention/procedure (minutes, hours or days).
4. Details of who will conduct the intervention/procedure, and where it will take place.

Intervention or procedure	1	2	3	4
Vital Signs	16	16	5	Vital signs to be checked at baseline and at each treatment visit (3 measurements before, during and after each infusion), with additional checks at week 2 and 6 (in between the first 2 cycles)
WHO Performance Status	34	34	10	WHO Performance Status to be checked at screening, baseline, each treatment visit and throughout follow-up phase
Height and weight	16	16	5	Height and weight to be checked at baseline and at each treatment visit, with additional checks at week 2 and 6 (in between the first 2 cycles)
Con-medication history	18	18	5	Con-meds to be checked at baseline and at each treatment visit, with additional checks at week 2, 6 (in between the first 2 cycles), week 52 and month 15
CT Scan with contrast (Chest Abdomen Pelvis)	15	14	60	Pre-surgery and post-surgery CT scan as per current SOC in RCC. BAUS guidelines recommend CT scans at regular intervals for patients with intermediate to high risk of recurrence post-nephrectomy but there is no consensus on the actual schedule. Within our Trial Development Group, which has members from various university hospitals in the UK, the consensus is that the proposed RAMPART CT schedule is in line with local SOC protocols. This might vary at other smaller participating centres. Monitoring scans as per BAUS guidelines. There is no consensus regarding the timing of monitoring scans but it is accepted standard-of-care to actively monitoring patients post-surgery
Blood test (clinical biochemistry, haematology, Hep C, INR and random cortisol)	18	18	5	Blood tests to be performed to assess eligibility and patient's safety before each treatment administration and up to 90 days after last treatment infusion. Arm A patients will also have regular blood tests but these will coincide with visits required for CT scans (11 visits for a patients up to year 10 FU visit)
Durvalumab infusion (Arm B and C patients)	13	13	60	Infusion to be administered in Outpatient clinics/Chemo Unit Monitoring of vital signs will be carried out before, during and after (30 minutes) the infusion

Tremelimumab infusion (Arm C patients only)	2	2	60	Infusion to be administered in Outpatient clinics/Chemo Unit Monitoring of vital signs will be carried out before, during and after (30 minutes) the infusion
Baseline blood sample (translational research question)	1	0	10	Collection of 1 EDTA sample for DNA analysis in Outpatient clinics by delegated clinical research staff
Physical examination	34	34	10	Physical examination to be undertaken at screening, baseline, each treatment visit and throughout follow-up phase
Adverse events	18	18	10	Adverse events to be assessed by the clinical team at each treatment visit and up to 90 days after last protocol infusion (week 52 and month 15)
ECG	2	1	10	ECG to be performed at screening and prior to the first infusion
Pregnancy test (urine or serum)	16	15	5	Pregnancy tests to be performed (female participants only) at screening, prior to each treatment administration and 6 months after last protocol treatment

A20. Will you withhold an intervention or procedure, which would normally be considered a part of routine care?

○ Yes ◉ No

A21. How long do you expect each participant to be in the study in total?

Patients randomised to Arm B or C will undergo treatment for 1 year maximum. Patients randomised to Arm A will be in active monitoring for 1 year in line with current standard-of-care for renal carcinoma after nephrectomy.

Follow-up of all randomised patients (Arm A, B or C) will start from the point of randomisation and continue until the Overall Survival endpoint has been reached and the data has been analysed.

A22. What are the potential risks and burdens for research participants and how will you minimise them?

For all studies, describe any potential adverse effects, pain, discomfort, distress, intrusion, inconvenience or changes to lifestyle. Only describe risks or burdens that could occur as a result of participation in the research. Say what steps would be taken to minimise risks and burdens as far as possible.

Side effects emerging from the administration of the experimental treatments might occur; these could be infusion related reactions or side effects arising more long term during the treatment phase. Close monitoring of all vital signs will take place before, during and after the infusions are administered. Details on side effects will be collected at each regular follow-up assessment. Participants will be encouraged at the time of informed consent and throughout participation to contact the local study team should any side effect or concern arise. A list of the most common and serious side effects will be provided in the Patient Information Sheet so that participants can remain vigilant.

Detailed toxicity management guidelines will be provided to the local study team as well as training prior to the study opening at the site. Safety blood tests will be repeated throughout the treatment phase and up to 90 days after last protocol infusion to ensure the participant's wellbeing is closely monitored, as described in section A19.

An Independent Data Monitoring Committee will review the accumulating data every 6 months to ensure the trial can respond quickly and stop recruitment if safety concerns emerge or a lack-of-benefit is observed.

The drawing of blood may cause pain, bruising, skin or vein irritation, blood-clot formation, bleeding, bleeding from the injection site, or infection. Although the risk of side effects from blood tests is higher for participants randomised to the experimental arms due to repeated safety assessments, the potential impact and burden is hoped to be relatively minor and not clinically severe.

There is also a small chance of reaction from the dye used for your routine CT scans; this risk is however small and not significantly above the current standard-of-care as CT scanning is part of the active monitoring required by the current NICE guidelines.

All treatment or test-related risks have been described in the Patient Information Sheet to ensure potential participants are adequately informed.

A23. Will interviews/ questionnaires or group discussions include topics that might be sensitive, embarrassing or upsetting, or is it possible that criminal or other disclosures requiring action could occur during the study?

◉ Yes ○ No

If Yes, please give details of procedures in place to deal with these issues:

Quality of Life (EORTC QLQ-C30), Health Economics (EORTC EQ-5D) and Preferences for Adjuvant Immunotherapy in RAMPART (PAIR) questionnaires will be completed by patients who have agreed to take part in the Patient Report Outcome sub-studies at the point of consent. Participation in each of these sub-studies is voluntary.

All questionnaires will be anonymised and the trial team at the MRC CTU at UCL will not be able to access any direct, personal information on the participant completing the questionnaires.

Furthermore, given the sensitivity of the questions asked (mobility and physical condition, self-care, daily activities, pain and discomfort, anxiety and depression), the TDG agreed that administration should not continue after disease progression.

A24. What is the potential for benefit to research participants?

Participants will have access to novel cancer immunotherapy treatments that might potentially be shown to be beneficial to delay recurrence and prolong survival in a setting where the current standard-of-care does not offer any alternative therapies.

As participants will be assessed more frequently than standard-of-care, there is the potential for recurrences in some patients to be detected earlier, allowing more prompt access to treatments for advanced kidney cancer.

The review of the protocol and PIS by the MRC CTU at UCL Patient Representative (part of the MRC CTU at UCL Protocol Review Committee) highlighted how, although individual participants might not gain any direct benefit, the information and data generated by the trial will contribute to the potential change in the standard-of-care for kidney cancer and benefit the national cancer strategy.

A25. What arrangements are being made for continued provision of the intervention for participants, if appropriate, once the research has finished? *May apply to any clinical intervention, including a drug, medical device, mental health intervention, complementary therapy, physiotherapy, dietary manipulation, lifestyle change, etc.*

Study participants will undergo experimental treatment for a maximum of 1 year or until progression. Patients who present with disease progression will be able to access first line therapies for metastatic renal carcinoma as recommended by NICE.

A26. What are the potential risks for the researchers themselves? *(if any)*

None

RECRUITMENT AND INFORMED CONSENT

In this section we ask you to describe the recruitment procedures for the study. Please give separate details for different study groups where appropriate.

A27-1. How will potential participants, records or samples be identified? Who will carry this out and what resources will be used?*For example, identification may involve a disease register, computerised search of GP records, or review of medical records. Indicate whether this will be done by the direct healthcare team or by researchers acting under arrangements with the responsible care organisation(s).*

Potential participants will be identified as their diagnosis of renal cell carcinoma is confirmed and referral for

nephrectomy is commenced. Urology and oncology teams at accredited RAMPART centres across the UK will screen potential participants at Multi-Disciplinary Team meetings and in outpatient clinics by reviewing the patients' records (electronic or paper depending on the systems used locally).

Patients will be approached about the trial by delegated members of the direct care team. Once the informed consent process is completed (with the participant and clinician signing the trial consent form), all remaining screening tests (those not already included in routine clinical practice) will be performed and eligibility fully assessed.

Once eligibility has been confirmed, the participant will be informed to confirm continued willingness to be randomised into the trial. Randomisation will be conducted by delegated members of the clinical research team (e.g. research nurse or research coordinator) via a central randomisation system (details on the randomisation process can be found in the protocol).

A27-2. Will the identification of potential participants involve reviewing or screening the identifiable personal information of patients, service users or any other person?

○ Yes ◉ No

Please give details below:
Only the direct clinical care team will have access to patient records without explicit consent in order to identify potential participants.

A28. Will any participants be recruited by publicity through posters, leaflets, adverts or websites?

○ Yes ◉ No

A29. How and by whom will potential participants first be approached?

Discussion on potentially eligible participants will take place with the Multi Disciplinary Team (MDT) as the diagnosis of renal cell carcinoma is confirmed and referral for nephrectomy is initiated. Patients will be approached by delegated and appropriately trained members of the urology or oncology team in outpatient clinics. The informed consent process will begin at an initial consultation involving the clinical and clinical research team and the trial introduced. A copy of the current Patient Information Sheet will be provided to the potential participant for information and to support further evaluation.

A30-1. Will you obtain informed consent from or on behalf of research participants?

◉ Yes ○ No

If you will be obtaining consent from adult participants, please give details of who will take consent and how it will be done, with details of any steps to provide information (a written information sheet, videos, or interactive material). Arrangements for adults unable to consent for themselves should be described separately in Part B Section 6, and for children in Part B Section 7.

If you plan to seek informed consent from vulnerable groups, say how you will ensure that consent is voluntary and fully informed.

Informed consent will be taken from all potential participants who have expressed an interest in taking part in the trial and who, in the initial phases of the screening process, have been found to meet the broad eligibility criteria.

All aspects covered in the PIS will be explained in person at outpatient clinics and a copy of the approved PIS will be provided to the potential participant for further reading.

Before written informed consent is taken, the responsible and delegated member of the local clinical team will ascertain that the potential participants understands the following aspects of the trial:
1. The purpose and nature of the research.
2. What the research involves, its benefits, risks and burdens.
3. Participation is voluntary and deciding not to take part will not affect a patient's clinical care

Informed consent will only be taken from participants who are deemed to be capable to retain information about the

trial in order to make an effective decision, and are able to make a free choice.

Informed consent will be taken in writing by signing a copy of the approved trial consent form.

All activities required for the informed consent process will be carried out by delegated members of the clinical and/or clinical research team, who have undergone trial-specific training and been delegated to performed informed consent activities by the local Principal Investigator, as documented on the trial delegation log.

Details on the informed consent process will be included in the patient's notes and a copy of the fully signed consent form will be kept in the notes and an anonymised copy sent to the trial management team at the MRC CTU at UCL for central monitoring puporses.

If you are not obtaining consent, please explain why not.

N/A

Please enclose a copy of the information sheet(s) and consent form(s).

A30-2. Will you record informed consent (or advice from consultees) in writing?

(●) Yes ( ) No

A31. How long will you allow potential participants to decide whether or not to take part?

In order for a participant to be eligible, randomisation needs to take place between 28 and 91 days after surgery. All informed consent procedures will therefore need to take into consideration these timelines when approaching a patient.

As part of the informed consent process, the delegated member of staff will check with the potential participant whether more time is needed to make a decision. If more time is needed to reflect on all aspects of the trial, a minimum of 24 hours will be allowed before the participant is approached again. The most likely scenario in these cases would be for the patient to be approached at the next planned clinic visit, as long as this wouldn't result in exceeding the 28-91 days post-surgery timeline which would make the patient ineligible.

A32. Will you recruit any participants who are involved in current research or have recently been involved in any research prior to recruitment?

( ) Yes
(●) No
( ) Not Known

A33-1. What arrangements have been made for persons who might not adequately understand verbal explanations or written information given in English, or who have special communication needs?*(e.g. translation, use of interpreters)*

There are no immediate plans for translation of Patient Information Sheet and Consent form for non-English speaking participants in the UK (with the exception as described in A33-2 for Welsh-speaking participants). However, if Principal Investigators and local research teams report that this policy is excluding a number of potentially eligible participants, the Trial Management Group and trial team will re-assess and consider translation of all patient-related material.

A33-2. What arrangements will you make to comply with the principles of the Welsh Language Act in the provision of information to participants in Wales?

Participants who solely speak Welsh will receive a copy of the Patient Information Sheet (PIS) and Consent Form (CF) in the Welsh Language, translated by a translator from the Welsh Language Board.

The PIS and CF will be back translated in English by an official translator and back-translation certified by the Sponsor before being circulated to Welsh speaking participants. The CF has also been adapted to allow for an independent witness to confirm the informed consent process has taken place.

A34. What arrangements will you make to ensure participants receive any information that becomes available during the course of the research that may be relevant to their continued participation?

Newly available information from other relevant ongoing trials or from within the trial will be assessed by the Trial Management Group and discussion will take place over the relevance and impact to patients as well as an effective communication plan.

For new information impacting the safety, treatment or management of trial participants, an amendment to the protocol and PIS will be submitted to the Research Ethics Committee (REC) and disseminated to participants once a favourable opinion has been obtained by the REC and local NHS Management. Where necessary, previously recruited participants will then be approached for re-consent by the local clinical research team.

For newly available information that does not impact the safety, treatment or management of trial participants other channels of communications may be considered. Where appropriate a REC approved letter will be circulated to trial participants to inform them of any significant new information.

The trial website will be kept updated with all new information both about the trial and any information relevant to the wider population of patients affected by kidney cancer. The RAMPART trial website will allow trial participants and the wider population to subscribe to receive newsletters and updates about the trial. In order to contact patients, we will therefore be collecting their personal email address. This aspect of the trial will be entirely optional and patients can unsubscribe and have their personal data removed at any time. Please see section A36 for more information on confidentiality

CONFIDENTIALITY

In this section, personal data means any data relating to a participant who could potentially be identified. It includes pseudonymised data capable of being linked to a participant through a unique code number.

Storage and use of personal data during the study

A36. Will you be undertaking any of the following activities at any stage (including in the identification of potential participants)?*(Tick as appropriate)*

- [x] Access to medical records by those outside the direct healthcare team
- [ ] Access to social care records by those outside the direct social care team
- [x] Electronic transfer by magnetic or optical media, email or computer networks
- [x] Sharing of personal data with other organisations
- [x] Export of personal data outside the EEA
- [x] Use of personal addresses, postcodes, faxes, emails or telephone numbers
- [ ] Publication of direct quotations from respondents
- [ ] Publication of data that might allow identification of individuals
- [ ] Use of audio/visual recording devices
- [ ] Storage of personal data on any of the following:
  - [ ] Manual files (includes paper or film)
  - [ ] NHS computers
  - [ ] Social Care Service computers
  - [ ] Home or other personal computers
  - [ ] University computers
  - [ ] Private company computers
  - [ ] Laptop computers

Further details:
Direct, personal participant data will only be accessed by the RAMPART trial management team and members of relevant regulatory authorities during on site monitoring, auditing or inspection visits. These activities will be however limited to participants who have been randomised into the trial and have therefore given their consent for access to their personal data.

Directly Identifiable Data
We plan to collect the full name, NHS number and full postcode of each patient that participates in the RAMPART study. It is necessary to collect these directly identifiable data items in order to allow the MRC CTU at UCL to make requests to NHS Digital (https://www.digital.nhs.uk/) for long term follow-up. All patients will be required to consent to the provision and usage of their personal data for these purposes. It will be stored securely and separate from the trial database in the UCL data safe haven. Access to directly identifiable data will generally be restricted to key authorised personnel within the Data Management Systems Group. If at any point the trial team requires access to these data, this requirement would need to be reviewed and approved by the MRC CTU at UCL Research Governance Committee (RGC).

The RAMPART trial website will allow patients to subscribe to receive newsletters and updates about the trial. In order to contact patients, we will therefore be collecting their personal email address. This aspect of the trial will be entirely optional and patients can unsubscribe and have their personal data removed at any time. The email addresses will be stored separately from the trial database. Access to the email addresses will be restricted to only trial staff responsible for distributing the trial updates. Communication will be managed via a dedicated shared inbox and not via individuals' email accounts.

The collection of directly identifiable data, for the purpose of long-term follow-up and dissemination of trial information to patients, will be presented and described in the trial's Risk Assessment which will be reviewed by the Unit's Research Governance Committee (RGC) prior to the start of recruitment.

Indirectly Identifiable Data
We plan to collect the initials and date of birth of each patient that participates in the RAMPART study. The data will be provided via two methods. Initially these details will be communicated by the hospital staff during the randomisation phone call. They will then be recorded on all Case Report Forms (CRFs), alongside a unique trial-specific patient ID to allow the MRC CTU staff to verify the identity and ensure the data is attributed to the correct participant.

The CRFs are paper forms used to collect details of the treatment and follow-up of trial patients. The hospital staff is responsible for transcribing the patient notes onto the CRFs. Once completed the CRFs are sent by standard post to the MRC CTU.

Unlike the directly identifiable data, this data will be stored securely on the trial database. Physical copies of the CRFs will be retained and stored in locked filing cabinets. Access to both the trial database and storage cabinets will be restricted to appropriately trained MRC CTU staff and controlled by delegation logs.

Anonymised Data
We plan to collect copies of Consent Forms for all patients entered into the study for central monitoring purposes. All identifiable data will be removed/obscured by the hospital staff, apart from the patient signature which will need to be verified. The Consent Forms will be checked by staff at the MRC CTU at UCL to ensure that appropriate consent has been provided and all processes will be in line with MRC CTU Informed Consent Destruction Working Instruction (v2.0). The Consent Forms will be checked by staff at the MRC CTU at UCL to ensure that appropriate consent has been provided. The Consent Forms will then be stored securely on the premises.

We will collect the CT scan images from all of the radiological assessments conducted during the trial. Hospital staff will be required to upload the images through a secure website and the files will be stored on a secure server (DICOM images). All images will be anonymised by the participating centre but further anonymisation software will be incorporated into the upload process to ensure that any directly identifiable patient data is stripped out of the image files prior to the transfer; the patient's ID will be the only identifier linked to the images.

The plan described above has been reviewed and approved by UCL Data Protection Registration team (reference No Z6364106/2017/05/56).

A37. Please describe the physical security arrangements for storage of personal data during the study?

Any data transferred to the trial management team at MRC CTU at UCL will be stored safely in line with the Unit's SOP; in particular:

1. Access to building is restricted to members of staff with ID only
2. Trial Master File and completed Case Report Forms will be stored in locked cabinets using Traka system requiring key holding for access
3. Trial database access is limited to trained staff with user-specific log in.

A38. How will you ensure the confidentiality of personal data?*Please provide a general statement of the policy and procedures for ensuring confidentiality, e.g. anonymisation or pseudonymisation of data.*

The management of directly and indirectly identifiable data will be in line with the MRC CTU at UCL Standard Operating Procedure. Furthermore, the trial is registered with the UCL Data Protection Registration Service before the start of data collection (reference No Z6364106/2017/05/56). The collection of directly identifiable data, for the purpose of long-term follow-up and dissemination of trial information to patients, will be presented and described in the trial's Risk Assessment which will be reviewed by the MRC CTU at UCL Research Governance Committee (RGC) prior to the start of recruitment.

Further information is provided in answer A36.

A40. Who will have access to participants' personal data during the study? *Where access is by individuals outside the direct care team, please justify and say whether consent will be sought.*

Access to participants' records will be required by the RAMPART Trial Management Team (TMT) during routine monitoring visits. All RAMPART TMT members will be fully trained on monitoring practice, patient's confidentiality and data security prior to attending a monitoring visit.

Auditors from AstraZeneca, the EMA and the FDA might require on site access to participants' records for regulatory and inspection purposes.

Potential participants will be informed via the PIS and during the informed consent process. The PIS provides details on this eventuality arising and the Consent Form incorporates an explicit clause about these circumstances.

Storage and use of data after the end of the study

A41. Where will the data generated by the study be analysed and by whom?

The Sponsor will be the owner of the data generated by the trial. All data collection will be managed by the MRC CTU at UCL where the data will be processed and stored. All analyses described in the study protocol and statistical analysis plan will be performed by the MRC CTU at UCL.

Data release requests (from trials within the MRC CTU and external trials)will be managed as per MRC CTU SOP and requests requiring a formal assessment by TMG and approval by the Trial Steering Committee (TSC). A Data Sharing Agreement will be in place prior to the transfer of any individual patient data. It is foreseen that only control arm patients data will be shared during the trial, with research arms data being shared only once the trial has reported on the co-primary outcomes.

A42. Who will have control of and act as the custodian for the data generated by the study?

	Title	Forename/Initials	Surname
	Dr.	Angela	Meade
Post	Project Lead		
Qualifications	DPhil (Biomedical Sciences, University of Ulster) MSc (Clinical Trials, University of London) BSc (Biomedical Sciences, University of Ulster)		
Work Address	MRC Clinical Trials Unit at UCL Institute of Clinical Trials and Methodology 90 High Holborn		
Post Code	WC1V 6LJ		

Work Email	a.meade@ucl.ac.uk
Work Telephone	02076704761
Fax	02076704653

A43. How long will personal data be stored or accessed after the study has ended?

- ○ Less than 3 months
- ○ 3 – 6 months
- ○ 6 – 12 months
- ○ 12 months – 3 years
- ◉ Over 3 years

If longer than 12 months, please justify:
Full name, NHS number and full postcode will be collected to allow the Sponsor to make requests to NHS Digital (https://www.digital.nhs.uk/) for long term follow-up

In line with MRC guidelines on retention of identifiable data (http://www.mrc.ac.uk/documents/pdf/personal-information-in-medic al-research/) and Clinical Trial Regulation (No 536/2014), the Sponsor will store research records for at least 25 years to allow adequate time for review and re-appraisal and potential regulatory submission. As Overall Survival is one of the primary outcome, long term follow-up and mortality data is essential to conduct primary analysis.

A44. For how long will you store research data generated by the study?

Years: 25
Months:

A45. Please give details of the long term arrangements for storage of research data after the study has ended.*Say where data will be stored, who will have access and the arrangements to ensure security.*

Data will be stored in paper and electronic format until both co-primary endpoints have been reached and the final report for the trial has been generated.

A detailed description of the data management systems and their security settings is provided in A36 and A38

INCENTIVES AND PAYMENTS

A46. Will research participants receive any payments, reimbursement of expenses or any other benefits or incentives for taking part in this research?

○ Yes ◉ No

A47. Will individual researchers receive any personal payment over and above normal salary, or any other benefits or incentives, for taking part in this research?

○ Yes ◉ No

A48. Does the Chief Investigator or any other investigator/collaborator have any direct personal involvement (e.g. financial, share holding, personal relationship etc.) in the organisations sponsoring or funding the research that may give rise to a possible conflict of interest?

◯ Yes ◉ No

NOTIFICATION OF OTHER PROFESSIONALS

A49-1. Will you inform the participants' General Practitioners (and/or any other health or care professional responsible for their care) that they are taking part in the study?

◉ Yes ◯ No

If Yes, please enclose a copy of the information sheet/letter for the GP/health professional with a version number and date.

A49-2. Will you seek permission from the research participants to inform their GP or other health/ care professional?

◉ Yes ◯ No

It should be made clear in the participant's information sheet if the GP/health professional will be informed.

PUBLICATION AND DISSEMINATION

A50. Will the research be registered on a public database?

The Department of Health's Research Governance Framework for Health and Social Care and the research governance frameworks for Wales, Scotland and Northern Ireland set out the requirement for registration of trials. Furthermore: Article 19 of the World Medical Association Declaration of Helsinki adopted in 2008 states that "every clinical trial must be registered on a publicly accessible database before recruitment of the first subject"; and the International Committee of Medical Journal Editors (ICMJE) will consider a clinical trial for publication only if it has been registered in an appropriate registry. Please see guidance for more information.

◉ Yes ◯ No

Please give details, or justify if not registering the research.
The RAMPART trial is registered on the ISRCTN and ClinicalTrials.gov registries.

As the trial will be part of the NIHR CRN Portfolio, information will also be registered on the NIHR CRN Central Portfolio Management System upon completion of the adoption process.

Please ensure that you have entered registry reference number(s) in question A5-1.

A51. How do you intend to report and disseminate the results of the study? *Tick as appropriate:*

- ☑ Peer reviewed scientific journals
- ☐ Internal report
- ☑ Conference presentation
- ☑ Publication on website
- ☑ Other publication
- ☑ Submission to regulatory authorities
- ☐ Access to raw data and right to publish freely by all investigators in study or by Independent Steering Committee on behalf of all investigators
- ☐ No plans to report or disseminate the results
- ☐ Other (please specify)

A52. If you will be using identifiable personal data, how will you ensure that anonymity will be maintained when publishing the results?

N/A

No directly identifiable personal data will be published for trial participants

A53. Will you inform participants of the results?

(●) Yes ( ) No

Please give details of how you will inform participants or justify if not doing so.
As results emerge from the RAMPART trial, the Trial Management Team will create newsletters and summaries of the results in lay language to inform all trial participants and patients in general. These documents will be submitted to the REC for review and approval as required and disseminated to participants and patients via the local clinical team.

Patient-focused meetings will be organised by the Trial Management Team in collaboration with Kidney Cancer UK and Cancer Research UK to disseminate results to all interested trial participants and patients in general.

The trial website will also contain a participant-focused section where all users can be informed of the trial results and progress.

5. Scientific and Statistical Review

A54. How has the scientific quality of the research been assessed?*Tick as appropriate:*

- [x] Independent external review
- [ ] Review within a company
- [ ] Review within a multi−centre research group
- [ ] Review within the Chief Investigator's institution or host organisation
- [ ] Review within the research team
- [ ] Review by educational supervisor
- [ ] Other

Justify and describe the review process and outcome. If the review has been undertaken but not seen by the researcher, give details of the body which has undertaken the review:
The RAMPART trial underwent an independent, scientific peer-review by Kidney Cancer UK (KCUK) as part of a successful funding application to the charitable body. A letter by KCUK to confirm review process is enclosed with this application.

For all studies except non-doctoral student research, please enclose a copy of any available scientific critique reports, together with any related correspondence.

For non-doctoral student research, please enclose a copy of the assessment from your educational supervisor/ institution.

A56. How have the statistical aspects of the research been reviewed?*Tick as appropriate:*

- [x] Review by independent statistician commissioned by funder or sponsor
- [ ] Other review by independent statistician
- [ ] Review by company statistician
- [ ] Review by a statistician within the Chief Investigator's institution
- [ ] Review by a statistician within the research team or multi−centre group
- [ ] Review by educational supervisor
- [x] Other review by individual with relevant statistical expertise
- [ ] No review necessary as only frequencies and associations will be assessed – details of statistical input not required

In all cases please give details below of the individual responsible for reviewing the statistical aspects. If advice has been provided in confidence, give details of the department and institution concerned.

	Title Forename/Initials Surname
	Prof Mahesh Parmar
Department	MRC CTU at UCL Institute of Clinical Trials & Methodology
Institution	University College London
Work Address	2nd floor 90 High Holborn
Post Code	WC1V 6LJ
Telephone	+44 020 76704700
Fax	+44 020 76704818
Mobile	
E-mail	m.parmar@ucl.ac.uk

Please enclose a copy of any available comments or reports from a statistician.

A57. What is the primary outcome measure for the study?

The RAMPART trial has two co-primary outcome measures
1. Disease Free Survival (DFS)
2. Overall Survival (OS)

DFS is defined as the interval from randomisation to first evidence of local recurrence, new primary RCC, distant metastases, or death from any cause, whichever occurs first.

OS is defined as all-cause mortality, the time from randomisation to death from any cause (including RCC).

A58. What are the secondary outcome measures?*(if any)*

1. Metastasis-free survival (MFS) = the interval from randomisation to first evidence of metastases or death from RCC
2. RCC specific survival time = the interval from randomisation to death from RCC
3. Quality of life
4. Toxicity
5. Patient preferences for adjuvant immunotherapy

A59. What is the sample size for the research? *How many participants/samples/data records do you plan to study in total? If there is more than one group, please give further details below.*

Total UK sample size:	1175
Total international sample size (including UK):	1750
Total in European Economic Area:	200

Further details:
Recruitment to the RAMPART trial will be largely in the UK.

Participating centres will also be in France, USA, Australia and New Zealand; a breakdown of the planned accrual is detailed below

1. UK (1175)
2. Australia (150)
3. New Zealand (50)
4. USA (175)
5. France (200)

A60. How was the sample size decided upon? *If a formal sample size calculation was used, indicate how this was done, giving sufficient information to justify and reproduce the calculation.*

The sample size calculations and design characteristics for the RAMPART design were obtained using nstage (version 3.0.1, 10 Sep 2014). Specifically, the nstage program was used to obtain the target number of control arm events needed at each stage for each comparison and an approximate idea for the timing of the stages. Artpep (version 1.0.4 PR 05 Jul 2013) was then used to project a more realistic analysis timeline using accrual and time-to-event patterns (based on the SORCE trial). ART (version 1.1.0, 10 Dec 2013) was used to determine the absolute differences in DFS and/or OS at time t. All calculations were performed in Stata 14.1.

Using the SORCE trial control arm data, we anticipate a 3 year DFS rate of 65% on the control arm of RAMPART. We plan to recruit 1,750 patients (750 to Arm A, 500 to Arm B and 500 to Arm C) over approximately 5.5 years. At the start of recruitment, patients with Leibovich score 3-11 will be eligible for randomisation. We will monitor accrual and stop recruiting intermediate risk patients (Leibovich Score 3-5) after three years or when intermediate risk patients contribute 25% of the total accrual target, whichever is earlier. Intermediate risk patients will only be included in the early years of the trial when their recurrences will be expected to contribute to the DFS analysis. Recruitment of patients with Leibovich Score 6-11 will continue until the accrual target is reached.

A61. Will participants be allocated to groups at random?

(●) Yes ( ) No

If yes, please give details of the intended method of randomisation:
Patients will be randomised centrally using stratified block randomisation in the ratio of A3:B2:C2

A62. Please describe the methods of analysis (statistical or other appropriate methods, e.g. for qualitative research) by which the data will be evaluated to meet the study objectives.

The RAMPART trial uses a Multi-Arm Multi-Stage design; a number of pre-planned interim analysis with formal stopping guidelines will be performed during the trial for all ongoing comparisons. When a new research comparison is introduced to the trial platform, the statistical analysis plan will be updated to reflect the data analyses for the specific comparisons. None of the existing research comparisons will be affected by the introduction of new research comparisons.

A time-to-event analysis will be performed for all intermediate and primary outcome measures.

1st Safety Analysis: to be performed when 70 patients are enrolled in the trial or after 6 months from opening to recruitment, whichever is sooner

Disease Free Survival

Arm A vs Arm C (intermediate and high-risk patients)

Interim analysis 1: triggered by 197 events in the control arm and anticipated to occur approximately 4.75 years from opening to recruitment. An observed HR of > 0.831 will be taken as an indication of lack-of-benefit from the combination. A stopping guideline for overwhelming benefit is to observe a p-value of less than 0.001 (one sided)

Primary analysis: triggered by 276 events in the control arm anticipated to occur approximately 6.25 years from opening to recruitment. The target HR is 0.70 which translates to an absolute improvement in 3 year DFS of 9%

Arm A vs Arm B (intermediate and high-risk patients)

Interim analysis 1: triggered by 197 events in the control arm and anticipated to occur approximately 4.75 years from opening to recruitment. An observed HR of > 0.887 will be taken as an indication of lack-of-benefit from the durvalumab only research arm. A stopping guideline for overwhelming benefit is to observe a p-value of less than 0.001 (one sided)

Interim analysis 2: triggered by 277 events in the control arm and anticipated to occur approximately 6.25 years from opening to recruitment. An observed HR of > 0.864 will be taken as an indication of lack-of-benefit from Arm B. A stopping guideline for overwhelming benefit is to observe a p-value of less than 0.001 (one sided)

Interim analysis 3: Anticipated to occur approximately 8 years from opening to recruitment

Primary analysis: triggered by 416 events in the control arm anticipated to occur approximately 10.5 years from opening to recruitment. The target HR is 0.75 which translates to an absolute improvement in 3 year DFS of 7.4%

Overall survival (high-risk patients only)
Arm A vs Arm C: 940 high risk patients enrolled into the comparison; analysis expected to take place 13.25 years after trial commences. The target HR is 0.70 which translates to an absolute improvement in 5-year OS of 6.5%

Arm A vs Arm B: 940 high risk patients enrolled into the comparison; analysis expected to take place 20.25 years after trial commences. The target HR is 0.75 which translates to an absolute improvement in 5-year OS of 5.4%

6. MANAGEMENT OF THE RESEARCH

A63. Other key investigators/collaborators. *Please include all grant co−applicants, protocol co−authors and other key members of the Chief Investigator's team, including non-doctoral student researchers.*

	Title	Forename/Initials	Surname
	Prof	Thomas	Powles
Post	Medical Oncologist and TMG Vice-Chair		
Qualifications	MBBS, MRCP, MD		
Employer	Centre for Experimental Cancer Medicine		
Work Address	Barts Cancer Institute		
	Barts Health NHS Trust		
	London		
Post Code	EC1A 7BE		
Telephone			
Fax			
Mobile			
Work Email	Thomas.Powles@bartshealth.nhs.uk		

	Title	Forename/Initials	Surname
	Dr	Grant	Stewart
Post	Urological Surgeon and TMG Vice-Chair		
Qualifications	BSc(Hons), FRCSEd (Urol), MBChB, PhD		
Employer	University of Cambridge		
Work Address	Box 43, Addenbrooke's Hospital		
	Cambridge Biomedical Campus		
	Hill's Road, Cambridge, UK		
Post Code	CB2 0QQ		
Telephone			
Fax			
Mobile			
Work Email	gds35@cam.ac.uk		

	Title	Forename/Initials	Surname
	Dr	Paul	Nathan
Post	Medical Oncologist		
Qualifications	MBBS, PhD, FRCP		
Employer	Mount Vernon Cancer Centre		

Work Address	Rickmansworth Road Northwood, Middlesex UK
Post Code	HA6 2RN
Telephone	
Fax	
Mobile	
Work Email	p.nathan@nhs.net

Title	Forename/Initials	Surname
Prof	Brian	Rini

Post	Medical Oncologist
Qualifications	MD,FACP
Employer	Department of Hematology and Oncology
Work Address	Cleveland Clinic Taussig Cancer Institute 9500 Euclid Ave Cleveland, OH, USA
Post Code	44195
Telephone	
Fax	
Mobile	
Work Email	rinib2@ccf.org

Title	Forename/Initials	Surname
Dr	Toni	Choueiri

Post	Medical Oncologist
Qualifications	MD
Employer	Dana-Farber Cancer Institute
Work Address	Department of Medical Oncology 450 Brookline Ave Boston, MA, USA
Post Code	02215
Telephone	
Fax	
Mobile	
Work Email	Toni_Choueiri@DFCI.HARVARD.EDU

Title	Forename/Initials	Surname
Prof	Martin	Stockler

Post	Medical Oncologist
Qualifications	MBBS(Hons) MSc(Clin Epi) FRACP
Employer	University of Sydney
Work Address	NHMRC Clinical Trials Centre
Post Code	
Telephone	
Fax	
Mobile	
Work Email	martin.stockler@sydney.edu.au

	Title	Forename/Initials	Surname
	Prof	Ian	Davis
Post	Medical Oncologist		
Qualifications	MBBS (Hons) PhD FRACP FAChPM		
Employer	Monash University and Eastern Health		
Work Address	Melbourne Australia		
Post Code			
Telephone			
Fax			
Mobile			
Work Email	ian.davis@monash.edu		

	Title	Forename/Initials	Surname
	Dr	Laurance	Albiges
Post	Medical Oncologist		
Qualifications	MD, PhD		
Employer	Institut Gustave Roussy		
Work Address	114 Rue Edouard Vaillant Villejuif, France		
Post Code	94800		
Telephone			
Fax			
Mobile			
Work Email	Laurence.albiges@gustaveroussy.fr		

	Title	Forename/Initials	Surname
	Prof	David	Harrison
Post	Pathologist		
Qualifications			
Employer	School of Medicine		
Work Address	University of St Andrews St Andrews		
Post Code	KY16 9TF		
Telephone			
Fax			
Mobile			
Work Email	david.harrison@st-andrews.ac.uk		

	Title	Forename/Initials	Surname
	Mr	Alastair	Ritchie
Post	Urological Surgeon (retired)		
Qualifications			
Employer			
Work Address	UK		

Post Code	
Telephone	
Fax	
Mobile	
Work Email	

	Title	Forename/Initials	Surname
	Dr	Derfel	ap Dafydd
Post	Radiologist		
Qualifications	BSc MRCP FRCR		
Employer	Royal Marsden Hospital		
Work Address	London UK		
Post Code			
Telephone			
Fax			
Mobile			
Work Email	Derfel.Apdafydd@rmh.nhs.uk		

	Title	Forename/Initials	Surname
	Ms	Anita	McWhirter
Post	Pharmacist		
Qualifications			
Employer	Royal Marsden Hospital		
Work Address	London UK		
Post Code			
Telephone			
Fax			
Mobile			
Work Email			

	Title	Forename/Initials	Surname
	Dr	Pat	Hanlon
Post	Consumer Representative		
Qualifications	PhD		
Employer			
Work Address			
Post Code			
Telephone			
Fax			
Mobile			
Work Email	J.P.HANLON@bham.ac.uk		

	Title	Forename/Initials	Surname
	Ms	Christy	Watson
Post	Consumer Representative		
Qualifications			
Employer			
Work Address			
Post Code			
Telephone			
Fax			
Mobile			
Work Email	christyswankie@yahoo.co.uk		

	Title	Forename/Initials	Surname
	Ms	Sarah	Scovell
Post	Research Nurse		
Qualifications			
Employer	St Bartholomew's Hospital		
Work Address	London UK		
Post Code			
Telephone			
Fax			
Mobile			
Work Email	Sarah.Scovell@bartshealth.nhs.uk		

	Title	Forename/Initials	Surname
	Prof	Mahesh	Parmar
Post	Senior Statistician		
Qualifications	PhD		
Employer	University College London		
Work Address	90 High Holborn Institute of Clinical Trials & Methodology, MRC CTU at UCL London		
Post Code	WC1V 6LJ		
Telephone	+44 020 76704700		
Fax	+44 020 76704818		
Mobile			
Work Email	m.parmar@ucl.ac.uk		

	Title	Forename/Initials	Surname
	Prof	Richard	Kaplan
Post	Medical Oncologist and Programme Lead		
Qualifications	MD, FACP		
Employer	University College London		
Work Address	Institute of Clinical Trials & Methodology, MRC CTU at UCL 90 High Holborn London		

Post Code	WC1V 6LJ
Telephone	
Fax	
Mobile	
Work Email	r.kaplan@ucl.ac.uk

Title	Forename/Initials	Surname
Dr	Angela	Meade

Post	Project Lead
Qualifications	PhD
Employer	University College London
Work Address	Institute of Clinical Trials & Methodology, MRC CTU at UCL 90 High Holborn London
Post Code	WC1V 6LJ
Telephone	
Fax	
Mobile	
Work Email	a.meade@ucl.ac.uk

Title	Forename/Initials	Surname
Ms	Rahela	Choudhury

Post	Clinical Project Manager
Qualifications	
Employer	University College London
Work Address	Institute of Clinical Trials & Methodology, MRC CTU at UCL 90 High Holborn London
Post Code	WC1V 6LJ
Telephone	
Fax	
Mobile	
Work Email	rahela.choudhury@ucl.ac.uk

Title	Forename/Initials	Surname
Mr	Ben	Smith

Post	Trial Manager
Qualifications	BSc
Employer	University College London
Work Address	Institute of Clinical Trials & Methodology, MRC CTU at UCL 90 High Holborn London
Post Code	WC1V 6LJ
Telephone	
Fax	
Mobile	
Work Email	ben.m.smith@ucl.ac.uk

	Title	Forename/Initials	Surname
	Dr	Francesca	Schiavone
Post	Trial Manager		
Qualifications	PhD		
Employer	University College London		
Work Address	Institute of Clinical Trials & Methodology, MRC CTU at UCL 90 High Holborn London		
Post Code	WC1V 6LJ		
Telephone			
Fax			
Mobile			
Work Email	f.schiavone@ucl.ac.uk		

	Title	Forename/Initials	Surname
	Mr	Nat	Thorogood
Post	Data Manager		
Qualifications			
Employer	University College London		
Work Address	Institute of Clinical Trials & Methodology, MRC CTU at UCL 90 High Holborn London		
Post Code	WC1V 6LJ		
Telephone			
Fax			
Mobile			
Work Email	n.thorogood@ucl.ac.uk		

	Title	Forename/Initials	Surname
	Mr	Jiaull	jiaull.hussain.15@ucl.ac.uk
Post	Data Manager		
Qualifications	MSc		
Employer	University College London		
Work Address	Institute of Clinical Trials & Methodology, MRC CTU at UCL 90 High Holborn London		
Post Code	WC1V 6LJ		
Telephone			
Fax			
Mobile			
Work Email	jiaull.hussain.15@ucl.ac.uk		

	Title	Forename/Initials	Surname
	Dr	Louise	Choo
Post	Statistician		
Qualifications	PhD		
Employer	University College London		
Work Address	Institute of Clinical Trials & Methodology, MRC CTU at UCL 90 High Holborn London		

Post Code	WC1V 6LJ
Telephone	
Fax	
Mobile	
Work Email	louise.choo@ucl.ac.uk

A64. Details of research sponsor(s)

A64-1. Sponsor

SP1

Status:
- ○ NHS or HSC care organisation
- ◉ Academic
- ○ Pharmaceutical industry
- ○ Medical device industry
- ○ Local Authority
- ○ Other social care provider (including voluntary sector or private organisation)
- ○ Other

Commercial status: Non-Commercial

If Other, please specify:

Contact person

Name of organisation	University College London
Given name	Mahesh
Family name	Parmar
Address	Institute of Clinical Trials & Methodology, MRC CTU at UCL
Town/city	London
Post code	WC1V 6LJ
Country	UNITED KINGDOM
Telephone	+44 020 76704700
Fax	+44 020 76704818
E-mail	m.parmar@ucl.ac.uk

Legal representative in the European Economic Area for the purpose of this trial
A legal representative must be appointed for a clinical trial of an investigational medicinal product if the sponsor is not established within the European Economic Area (EEA) (see article 19 of Directive 2001/20/EC). If this applies, please enclose evidence that the legal representative is established within the EEA and has accepted the role of legal representative.

Legal representative

Contact person

Name of organisation	
Given name	
Family name	
Address	

Town/city
Post code
Country
Telephone
Fax
E-mail

A65. Has external funding for the research been secured?

- [x] Funding secured from one or more funders
- [ ] External funding application to one or more funders in progress
- [ ] No application for external funding will be made

What type of research project is this?

- (•) Standalone project
- ( ) Project that is part of a programme grant
- ( ) Project that is part of a Centre grant
- ( ) Project that is part of a fellowship/ personal award/ research training award
- ( ) Other

Other – please state:

Please give details of funding applications.

Organisation	Kidney Cancer UK
Address	The Old Coach House 56 High Street Harston, Cambridge
Post Code	CB22 7PZ
Telephone	01223 870008
Fax	
Mobile	
Email	

Funding Application Status: (•) Secured ( ) In progress

Amount: 12000 pa

Duration
Years: 20
Months: 0

If applicable, please specify the programme/ funding stream:

What is the funding stream/ programme for this research project?

Organisation	AstraZeneca UK LTD
Address	2 Kingdom Street London
Post Code	W2 6BD
Telephone	0800 783 0033
Fax	
Mobile	
Email	kathleen.bender@astrazeneca.com

Funding Application Status: ○ Secured ◉ In progress

Date Funding decision expected: 01/11/2017

Amount: £15.2million

Duration

Years: 20

Months: 0

If applicable, please specify the programme/ funding stream:

What is the funding stream/ programme for this research project?

A66. Has responsibility for any specific research activities or procedures been delegated to a subcontractor (other than a co-sponsor listed in A64-1) ? *Please give details of subcontractors if applicable.*

○ Yes ◉ No

A67. Has this or a similar application been previously rejected by a Research Ethics Committee in the UK or another country?

○ Yes ◉ No

Please provide a copy of the unfavourable opinion letter(s). You should explain in your answer to question A6-2 how the reasons for the unfavourable opinion have been addressed in this application.

A68-1. Give details of the lead NHS R&D contact for this research:

Title	Forename/Initials	Surname
	Jane	Lawrence

Organisation	Royal Marsden NHS Foundation Trust
Address	Clinical R&D Office Royal Marsden NHS Foundation Trust Downs Road, Sutton
Post Code	SM2 5PT
Work Email	research.development@rmh.nhs.uk
Telephone	0208 661 3882
Fax	
Mobile	

Details can be obtained from the NHS R&D Forum website: http://www.rdforum.nhs.uk

A68-2. Select Local Clinical Research Network for NHS Organisation identified in A68-1:

South London

For more information, please refer to the question specific guidance.

A69-1. How long do you expect the study to last in the UK?

Planned start date: 02/01/2018
Planned end date: 01/01/2038
Total duration:
Years: 20 Months: 0 Days: 0

A69-2. How long do you expect the study to last in all countries?

Planned start date: 02/01/2018
Planned end date: 01/01/2038
Total duration:
Years: 20 Months: 0 Days: 0

A70. Definition of the end of trial, and justification in the case where it is not the last visit of the last subject undergoing the trial (1)

The trial will close when all patients have completed follow-up and all data queries have been resolved.

A71-1. Is this study?

- ○ Single centre
- ◉ Multicentre

A71-2. Where will the research take place? *(Tick as appropriate)*

- ☑ England
- ☑ Scotland
- ☑ Wales
- ☑ Northern Ireland
- ☑ Other countries in European Economic Area

Total UK sites in study 70

Number of sites anticipated in the Community 20

Does this trial involve countries outside the EU?

◉ Yes ○ No

☑ USA

☑ Other international (please specify)

Australia and New Zealand

A72. Which organisations in the UK will host the research? *Please indicate the type of organisation by ticking the box and give approximate numbers if known:*

☑ NHS organisations in England	60
☑ NHS organisations in Wales	5
☑ NHS organisations in Scotland	4
☑ HSC organisations in Northern Ireland	1
☐ GP practices in England	
☐ GP practices in Wales	
☐ GP practices in Scotland	
☐ GP practices in Northern Ireland	
☐ Joint health and social care agencies (eg community mental health teams)	
☐ Local authorities	
☐ Phase 1 trial units	
☐ Prison establishments	
☐ Probation areas	
☐ Independent (private or voluntary sector) organisations	
☐ Educational establishments	
☐ Independent research units	
☐ Other (give details)	
Total UK sites in study:	70

A73-1. Will potential participants be identified through any organisations other than the research sites listed above?

○ Yes ◉ No

A74. What arrangements are in place for monitoring and auditing the conduct of the research?

A risk-based central and on site monitoring will be carried out throughout the course of the trial. A budget will be in place to carry out up to 60 site monitoring visits per year. The trial's Quality Management and Monitoring Plan (QMMP) will set out all quality assurance procedures in line with the trial's Risk Assessment. Formal triggers will be used to guide both central and on site monitoring.

A75-1. What arrangements will be made to review interim safety and efficacy data from the trial? Will a formal data monitoring committee or equivalent body be convened?

An Independent Data Monitoring Committee (IDMC) will be responsible for the interim and final review of the trial data. The IDMC will be formed of clinicians with urological and oncologic expertise and at least one independent statistician. A Charter will be circulated and signed prior to the first IDMC meeting taking place. The IDMC will meet at least 6-monthly via teleconference and in person.

A Trial Steering Committee (TSC) will also be in place and act as executive oversight body for the trial. An umbrella GU TSC based at the MRC CTU and made of independent members will review all IDMC recommendations and ratify them as required. A Charter will be circulated and signed prior to the first TSC meeting taking place. The TSC will meet

at least 6-monthly following IDMC review via teleconference and in person.

If a formal DMC is to be convened, please forward details of the membership and standard operating procedures to the Research Ethics Committee when available. The REC should also be notified of DMC recommendations and receive summary reports of interim analyses.

A75-2. What are the criteria for electively stopping the trial or other research prematurely?

Details on formal stopping guidelines are provided in A62

A76. Insurance/ indemnity to meet potential legal liabilities

***Note:* in this question to NHS indemnity schemes include equivalent schemes provided by Health and Social Care (HSC) in Northern Ireland**

A76-1. What arrangements will be made for insurance and/or indemnity to meet the potential legal liability of the sponsor(s) for harm to participants arising from the management of the research? *Please tick box(es) as applicable.*

Note: Where a NHS organisation has agreed to act as sponsor or co-sponsor, indemnity is provided through NHS schemes. Indicate if this applies (there is no need to provide documentary evidence). For all other sponsors, please describe the arrangements and provide evidence.

- ☐ NHS indemnity scheme will apply (NHS sponsors only)
- ☑ Other insurance or indemnity arrangements will apply (give details below)

Please enclose a copy of relevant documents.

A76-2. What arrangements will be made for insurance and/ or indemnity to meet the potential legal liability of the sponsor(s) or employer(s) for harm to participants arising from the design of the research? *Please tick box(es) as applicable.*

Note: Where researchers with substantive NHS employment contracts have designed the research, indemnity is provided through NHS schemes. Indicate if this applies (there is no need to provide documentary evidence). For other protocol authors (e.g. company employees, university members), please describe the arrangements and provide evidence.

- ☐ NHS indemnity scheme will apply (protocol authors with NHS contracts only)
- ☑ Other insurance or indemnity arrangements will apply (give details below)

Please enclose a copy of relevant documents.

A76-3. What arrangements will be made for insurance and/ or indemnity to meet the potential legal liability of investigators/collaborators arising from harm to participants in the conduct of the research?

Note: Where the participants are NHS patients, indemnity is provided through the NHS schemes or through professional indemnity. Indicate if this applies to the whole study (there is no need to provide documentary evidence). Where non-NHS sites are to be included in the research, including private practices, please describe the arrangements which will be made at these sites and provide evidence.

- ☑ NHS indemnity scheme or professional indemnity will apply (participants recruited at NHS sites only)
- ☐ Research includes non-NHS sites (give details of insurance/ indemnity arrangements for these sites below)

Please enclose a copy of relevant documents.

A77. Has the sponsor(s) made arrangements for payment of compensation in the event of harm to the research participants where no legal liability arises?

(●) Yes ( ) No

If Yes, please give details of the compensation policy:
UCL hold an insurance policy to provide for the payment of compensation to research participants where legal liability (negligence) arises of UCL and its employees or agents in relation to claims made by, and for non-negligent harm to, clinical trial participants in the study insured.

UCL's agreements with individual trial sites require the sites to hold NHS indemnity, or to be part of another insurance scheme, to meet their own legal liabilities.

Please enclose a copy of relevant documents.

A78. Could the research lead to the development of a new product/process or the generation of intellectual property?

( ) Yes ( ) No (●) Not sure

Part B Section 1: Investigational Medicinal Products

Information on each IMP.

Information on each 'bulk product' before trial-specific operations (blinding, trial specific packaging and labelling) should be provided in this section for each investigational medicinal product (IMP) being tested including each comparator, if applicable.
If the trial is performed with several products please create a separate set of the following questions for each product. If the product is a combination product please give separate information for each active substance.
Click on the first row and enter details of the product in the following screens. When you have completed the details, click on the navigate button or the "See All" link and return to this section to enter details of the next product. When you have completed details of all products please move to question 13 using the navigation screen.

Investigational medicinal products

PR1 Durvalumab

PR2 Tremelimumab

13. Indicate which of the following is described below then repeat as necessary for each:

This refers to the IMP number: **PR1**
Investigational medicinal product category:
Test IMP

14. STATUS OF THE IMP
If the IMP has a marketing authorisation in the Member State concerned by this application but the trade name and marketing authorisation holder are not fixed in the protocol, go to question 14-.2

14-1. Does the IMP to be used in the trial have a marketing authorisation?

◯ Yes ◉ No ◯ Not Answered

14-2. Situations where an IMP to be used in the CT has a MA in the MS concerned, but the protocol allows that any brand of the IMP with a MA in that MS be administered to the trial subjects and it is not possible to clearly identify the IMP(s) in advance of the trial start

In the protocol, is treatment defined only by active substance?
◯ Yes ◉ No ◯ Not Answered

In the protocol, do treatment regimens allow different combinations of marketed products used according to local clinical practice at some or all investigator sites in the MS?
◯ Yes ◉ No ◯ Not Answered

The products to be administered as IMPs are defined as belonging to an ATC group
◯ Yes ◉ No ◯ Not Answered

Other :
◯ Yes ◉ No ◯ Not Answered

14-3. IMPD submitted:

Full IMPD

○ Yes ◉ No ○ Not Answered

Simplified IMPD

◉ Yes ○ No ○ Not Answered

Provide justification for using simplified dossier in the covering letter

Summary of product characteristics (SmPC) only

○ Yes ◉ No ○ Not Answered

14-4. Has the use of the IMP been previously authorised in a clinical trial conducted by the sponsor in the Community?

○ Yes ◉ No ○ Not Answered

14-5. Has the IMP been designated in this indication as an orphan drug in the Community?

○ Yes ◉ No ○ Not Answered

14-6. Has the IMP been the subject of scientific advice related to this clinical trial?

◉ Yes ○ No ○ Not Answered

Please indicate source of advice and provide a copy in the CTA request:

From the CHMP?

◉ Yes ○ No ○ Not Answered

CHMP = Committee for Medicinal Products for Human Use

From a MS competent authority?

○ Yes ◉ No ○ Not Answered

This is a sub-set of questions about each IMP. To return to the list of IMPs select "See all" at the top of the page or select "Navigate". To complete further questions about this IMP select "Next".

Description of IMP

15-1. Description of IMP

Product name where applicable	Durvalumab
Product code where applicable	MEDI4736
ATC codes, if officially registered	L01XC28
Pharmaceutical form (use standard terms)	Concentrate and diluent for solution for infusion
Is this a specific paediatric formulation?	○ Yes ◉ No ○ Not Answered
Maximum duration of treatment of a subject according to the protocol	1 year maximum; 13 cycles in total. Cycle defined as 28 days with infusion on Day 1 of each cycle

Dose allowed

First dose for first-in-human clinical trial	
Specify per day or total:	◯ per day ◯ total ◉ Not Answered
Specify total dose (number and unit)	
Route of administration (relevant to the first dose):	

Maximum dose allowed	1500 mg per infusion 28 day cycle with infusion on day 1
Specify per day or total	◉ per day ◯ total ◯ Not Answered
Specify total dose (number and unit)	53.57 mg milligram(s)
Route of administration (relevant to the maximum dose):	Intravenous Use

Routes of administration for this IMP

Intravenous Use

This is a sub-set of questions about each IMP. To return to the list of IMPs select "See all" at the top of the page or select "Navigate". To complete further questions about this IMP select "Next".

15-2. Active substances

Complete all fields that currently apply to this Active Substance in this Product. If you have IMPs with different concentrations of the Active Substance complete a new Sub-section D for each.

Active Substance 1

Name of active substance (INN or proposed INN if available):	Durvalumab
CAS number:	1428935-60-7
Current sponsor code:	
Other descriptive name:	
Full Molecular formula	C6502H10018N1742O2024S42
Chemical/biological description of the Active Substance	Human immunoglobulin (Ig) G1 kappa (IgG1κ) monoclonal antibody (mAb) that blocks the interaction of programmed cell death ligand 1 (PD-L1) (but not programmed cell death ligand-2) with programmed cell death 1 (PD-1) on T-lymphocyte (T-cells) and cluster of differentiation (CD)80 (B7.1) on immune cells (IC) and is engineered to reduce antibody-dependent cell-mediated cytotoxicity (ADCC).

Strength

Concentration unit:	mg/ml milligram(s)/millilitre
Concentration type:	equal
Concentration number (only use both fields for range):	50

15-3. Type of IMP

Does the IMP contain an active substance:

Of chemical origin?	○ Yes	◉ No	○ Not Answered
Of biological / biotechnological origin?(other than Advanced Therapy IMP (ATIMP))	◉ Yes	○ No	○ Not Answered
Is this a:			
Advanced Therapy IMP (ATIMP) [1]	○ Yes	◉ No	○ Not Answered
Combination product that includes a device, but does not involve an Advanced Therapy	○ Yes	◉ No	○ Not Answered
Radiopharmaceutical medicinal product?	○ Yes	◉ No	○ Not Answered
Immunological medicinal product (e.g. vaccine, allergen, immune serum)?	○ Yes	◉ No	○ Not Answered
Plasma derived medicinal product?	○ Yes	◉ No	○ Not Answered
Extractive medicinal product?	○ Yes	◉ No	○ Not Answered
Recombinant medicinal product?	○ Yes	◉ No	○ Not Answered
Medicinal product containing genetically modified organisms?	○ Yes	◉ No	○ Not Answered
Herbal medicinal product?	○ Yes	◉ No	○ Not Answered
Homeopathic medicinal product?	○ Yes	◉ No	○ Not Answered
Another type of medicinal product?	○ Yes	◉ No	○ Not Answered

Specify the mode of action for the active substance in this medicinal product
The mode of action should briefly describe the chemical, biochemical, immunological or biological means that the IMP uses to effect its pharmaceutical action. Durvalumab is a human immunoglobulin (Ig) G1 kappa (IgG1κ) monoclonal antibody (mAb) that blocks the
interaction of programmed cell death ligand 1 (PD-L1) (but not programmed cell death ligand-2) with programmed cell death 1 (PD-1) on T-lymphocyte (T-cells) and cluster of differentiation (CD)80 (B7.1) on immune cells (IC) and is engineered to reduce antibody-dependent cell-mediated cytotoxicity (ADCC).

Is it an IMP to be used in a first-in-human clinical trial?	○ Yes	◉ No	○ Not Answered

[1,2,3,4,5] Complete sections D.4, D.5, D.6. and D.7, as applicable
[2,3] As defined in Annex 1 part IV of Directive 2001/83/EC as amended
[4] As defined in Article 2(1)(b) of Regulation 1394/2007/EC
[6] Guideline on strategies to identify and mitigate risks for first-in-human clinical trials with investigational medicinal products. EMEA/CHMP/SWP/28367/2007

13. Indicate which of the following is described below then repeat as necessary for each:

This refers to the IMP number: **PR2**
Investigational medicinal product category:
Test IMP

14. STATUS OF THE IMP
If the IMP has a marketing authorisation in the Member State concerned by this application but the trade name and marketing authorisation holder are not fixed in the protocol, go to question 14-.2

14-1. Does the IMP to be used in the trial have a marketing authorisation?

◯ Yes ◉ No ◯ Not Answered

14-2. Situations where an IMP to be used in the CT has a MA in the MS concerned, but the protocol allows that any brand of the IMP with a MA in that MS be administered to the trial subjects and it is not possible to clearly identify the IMP(s) in advance of the trial start

In the protocol, is treatment defined only by active substance?
◯ Yes ◉ No ◯ Not Answered

In the protocol, do treatment regimens allow different combinations of marketed products used according to local clinical practice at some or all investigator sites in the MS?
◯ Yes ◉ No ◯ Not Answered

The products to be administered as IMPs are defined as belonging to an ATC group
◯ Yes ◉ No ◯ Not Answered

Other :
◯ Yes ◉ No ◯ Not Answered

14-3. IMPD submitted:

Full IMPD
◯ Yes ◉ No ◯ Not Answered

Simplified IMPD
◉ Yes ◯ No ◯ Not Answered

Provide justification for using simplified dossier in the covering letter

Summary of product characteristics (SmPC) only
◯ Yes ◉ No ◯ Not Answered

14-4. Has the use of the IMP been previously authorised in a clinical trial conducted by the sponsor in the Community?

◯ Yes ◉ No ◯ Not Answered

14-5. Has the IMP been designated in this indication as an orphan drug in the Community?

◯ Yes ◉ No ◯ Not Answered

14-6. Has the IMP been the subject of scientific advice related to this clinical trial?

(●) Yes ( ) No ( ) Not Answered

Please indicate source of advice and provide a copy in the CTA request:

From the CHMP?

(●) Yes ( ) No ( ) Not Answered

CHMP = Committee for Medicinal Products for Human Use

From a MS competent authority?

( ) Yes (●) No ( ) Not Answered

This is a sub-set of questions about each IMP. To return to the list of IMPs select "See all" at the top of the page or select "Navigate". To complete further questions about this IMP select "Next".

Description of IMP

15-1. Description of IMP

Product name where applicable	Tremelimumab
Product code where applicable	CP-675,206 (formerly), MEDI1123
ATC codes, if officially registered	None
Pharmaceutical form (use standard terms)	Concentrate and diluent for solution for infusion
Is this a specific paediatric formulation?	( ) Yes (●) No ( ) Not Answered
Maximum duration of treatment of a subject according to the protocol	2 cycles maximum; Cycle defined as 28 days with infusion on Day 1 of each cycle

Dose allowed

First dose for first-in-human clinical trial	
Specify per day or total:	( ) per day ( ) total (●) Not Answered
Specify total dose (number and unit)	
Route of administration (relevant to the first dose):	
Maximum dose allowed	75 mg per infusion 28 days cycles with infusion on Day 1 2 cycles maximum
Specify per day or total	(●) per day ( ) total ( ) Not Answered
Specify total dose (number and unit)	2.67 mg milligram(s)
Route of administration (relevant to the maximum dose):	Intravenous Use

Routes of administration for this IMP

Intravenous Use

This is a sub-set of questions about each IMP. To return to the list of IMPs select "See all" at the top of the page or select "Navigate". To complete further questions about this IMP select "Next".

15-2. Active substances

Complete all fields that currently apply to this Active Substance in this Product. If you have IMPs with different concentrations of the Active Substance complete a new Sub-section D for each.

Active Substance 1

Name of active substance (INN or proposed INN if available):	Tremelimumab
CAS number:	745013-59-6
Current sponsor code:	
Other descriptive name:	
Full Molecular formula	C6500H9974N1726O2026S52
Chemical/biological description of the Active Substance	Human IgG2 monoclonal antibody (mAb) directed against CTLA-4

Strength

Concentration unit:	mg/ml milligram(s)/millilitre
Concentration type:	equal
Concentration number (only use both fields for range):	20

15-3. Type of IMP

Does the IMP contain an active substance:

Of chemical origin?	○ Yes ◉ No ○ Not Answered
Of biological / biotechnological origin?(other than Advanced Therapy IMP (ATIMP))	◉ Yes ○ No ○ Not Answered

Is this a:

Advanced Therapy IMP (ATIMP) (1)	○ Yes ◉ No ○ Not Answered
Combination product that includes a device, but does not involve an Advanced Therapy	○ Yes ◉ No ○ Not Answered
Radiopharmaceutical medicinal product?	○ Yes ◉ No ○ Not Answered
Immunological medicinal product (e.g. vaccine, allergen, immune serum)?	○ Yes ◉ No ○ Not Answered
Plasma derived medicinal product?	○ Yes ◉ No ○ Not Answered
Extractive medicinal product?	○ Yes ◉ No ○ Not Answered
Recombinant medicinal product?	○ Yes ◉ No ○ Not Answered
Medicinal product containing genetically modified organisms?	○ Yes ◉ No ○ Not Answered
Herbal medicinal product?	○ Yes ◉ No ○ Not Answered

Homeopathic medicinal product? ◯ Yes ◉ No ◯ Not Answered

Another type of medicinal product? ◯ Yes ◉ No ◯ Not Answered

Specify the mode of action for the active substance in this medicinal product
The mode of action should briefly describe the chemical, biochemical, immunological or biological means that the IMP uses to effect its pharmaceutical action.
Tremelimumab blocks the inhibitory signal resulting from CTLA-4 binding to CD80/86, leading to prolongation and enhancement of T-cell activation and expansion.

Is it an IMP to be used in a first-in-human clinical trial? ◯ Yes ◉ No ◯ Not Answered

(1,2,3,4,5) Complete sections D.4, D.5, D.6. and D.7, as applicable
(2,3) As defined in Annex 1 part IV of Directive 2001/83/EC as amended
(4) As defined in Article 2(1)(b) of Regulation 1394/2007/EC
(6) Guideline on strategies to identify and mitigate risks for first-in-human clinical trials with investigational medicinal products. EMEA/CHMP/SWP/28367/2007

Information on Placebo

13. Is there a placebo:

◯ Yes ◉ No

Index of Sites where the qualified person certifies batch release

14. IMPs and placebos for which no responsible site needs to be identified:

This section is used to identify IMPs and placebos which:

- Have an MA in the EU **and**
- Are sourced from the EU market **and**
- Are used in the trial without modification (eg not overencapsulated) **and**
- The packaging and labeling is carried out for local use only as per article 9.2 of the Directive 2005/28/EC (GCP Directive).

If all the conditions above are met, then select below the IMPs and placebos to which this applies.

This section is dedicated to finished IMPs, i.e. medicinal products randomised, packaged, labelled and certified for use in the clinical trial. In the case of multiple sites indicate the product certified by each site.

15. Identify who is responsible in the Community for the certification of the finished IMPs.
Where the product does not have a MA in the EU, but is supplied in bulk and final packaging and labelling for local use is carried out in accordance with article 9.2. of Directive 2005/28/EC (GCP Directive) then enter the site where the product was finally certified for release by the Qualified Person for use in the clinical trial.

RS1

Both

Organisation	Fisher Clinical Services UK Limited
Address	Langhurstwood Road
Town/city	Horsham
Post code	RH12 4QD
Country	UNITED KINGDOM

Give the manufacturing authorisation number
18693

If no authorisation, give the reasons:

Select the relevant IMP(s) and Placebo(s) from the drop down lists.

IMP
PR1

IMP
PR2

PART B: Section 3 – Exposure to ionising radiation

Complete sub-sections A and/or B as applicable with input from relevant experts. It is advisable to discuss the proposed research at an early stage with (a) a Medical Physics Expert and (b) a Clinical Radiation Expert, who will carry out the required assessments for sub-sections C and D. The lead MPE can also facilitate the completion of sub-sections A and/or B if necessary.

1. Does the study involve exposure to radioactive materials?

○ Yes ◉ No

To update the response above, go to the Project Filter Question 2 'Does the study involve exposure to radioactive materials?' and select an option.

2. Does the study involve other diagnostic or therapeutic ionising radiation?

◉ Yes ○ No

A. Radioactive materials

Details of radioactive materials

B. Other ionising radiation

B1. Details of other ionising radiation

Give details by completing the table below:

Procedure	No of procedures	Estimated procedure dose *(use national Diagnostic Reference Levels where available)*
CT scan with contrast (Chest Abdomen Pelvis)	15(1 research, 14 standard of care)	20 mSv

C. Dose and risk assessment

C1. What is the total participant dose from all the exposures in A1 and/or B1, and what component of this is the additional dose over and above standard practice? What are the risks associated with these two doses (total and additional)?

The dose and risk assessment should be set out below. This should be prepared by a Medical Physics Expert (MPE) who is a registered clinical scientist registered with the Health Professions Council and has expertise relevant to the planned exposures. Where the study involves different types of exposure (for example, both radioactive materials and other ionising radiation, or more than one imaging method), advice may need to be sought from other MPEs with relevant expertise. The lead MPE should produce a combined assessment for the ethics committee, giving the names of any other MPEs who have contributed to the assessment. Further guidance is available by clicking on the information button or in the document "Approval of research involving ionising radiation", available here: http://www.nres.nhs.uk/applications/guidance/research-guidance/#ion

This study requires exposures to ionising radiation which are detailed in B1. The total protocol dose is 300 mSv in ten years. This is the longest period of time a subject is likely to be enrolled for. Some of the total radiation dose required by the study is additional to routine clinical care. A protocol dose of 300 mSv is equivalent to 120 years of average natural background radiation in the UK.

Ionising radiation can cause cell damage which may manifest itself as cancer after many years or decades. The risk of developing cancer as a consequence of taking part in this study is estimated as 2%. For comparison, the natural lifetime cancer incidence in the general population is about 50%.

Special attention must be paid to pregnant/potentially pregnant women or those who are breast feeding, or other potentially vulnerable groups.

C2. Declaration by lead Medical Physics Expert

I am satisfied that the information in sub-sections A and/or B and the assessment in sub-section C provide a reasonable estimate of the ionising radiation exposure planned in this research and the associated risks.

This section was signed electronically by elly castellano on 05/10/2017 11:38.

Job Title/Post:	consultant physicist
Organisation:	the royal marsden
Email:	elly.castellano@rmh.nhs.uk

C3. Details of person acting as lead Medical Physics Expert

	Title	Forename/Initials	Surname
		Isabel	Castellano
Post	Head of Diagnostic Radiology Physics Group		
Details of clinical scientist registration with the Health Professions Council:			
Registration no	CS00359		
Organisation	The Royal Marsden NHS Foundation Trust		
Address	Fulham Road		
Post Code	SW3 6JJ		
Telephone	020 7811 8083		
Fax	020 7811 2522		
Mobile			
Email	elly.castellano@rmh.nhs.uk		

D. Clinical assessment

This sub-section should be completed by a Clinical Radiation Expert (CRE) who is a registered doctor or dentist with clinical expertise relevant to the planned exposures. The assessment should cover potential exposure at all research sites, taking account of possible variation in normal clinical practice. Where the study involves different types of exposure (for example, both radiotherapy and other ionising radiation), advice may need to be sought from other CREs with relevant expertise. The lead CRE should produce a combined assessment for the ethics committee, giving the names of any other CREs who have contributed to the assessment. The guidance notes give advice to Chief Investigators on who can act as lead Clinical Radiation Expert (CRE) and advice for the CRE on the assessment of exposures having regard to IRMER.

Special attention must be paid to pregnant/potentially pregnant women or those who are breast feeding, or other potentially vulnerable groups.

D1. Will the exposure exceed the exposure that might be received as part of normal care at any proposed research site?

(●) Yes ( ) No

D2. Assessment of additional exposure

Explain how the planned exposure compares with normal practice and assess whether it is appropriate, using language comprehensible to a lay person. Consideration should be given to the specific objectives of the exposure, the characteristics of participants, the potential diagnostic or therapeutic benefits to the participant, the potential benefits to society, the risk to the participant and the availability of alternative techniques involving less, or no, ionising radiation.

If pregnant or breast-feeding mothers are to be studied give reasons and details of special radiation protection measures to be taken.

RAMPART is a phase III trial assessing new treatments in adult patients with resected primary renal cancer who are at intermediate and high-risk of relapse.

The clinical outlook and prognosis of all of the participants in this study is significantly lower compared to the general population.

They will receive some additional radiation burden, some of which is above that anticipated in routine clinical care.

The risk of harm from the additional radiation burden is provided by the MPE evaluation but this is justified since it is essential to provide objective radiological assessment during the trial.

D3. Declaration by lead Clinical Radiation Expert

I am satisfied that the exposure to ionising radiation planned in this research study (as defined in A1 and/or B1) is reasonable and that the risks are adequately described in the participant information sheet for the study.

This section was signed electronically by Dr Derfel ap Dafydd on 12/10/2017 18:55.

Job Title/Post:	Consultant Radiologist
Organisation:	Royal Marsden
Email:	derfelapdafydd@hotmail.com

D4. Details of lead Clinical Radiation Expert

	Title	Forename/Initials	Surname
	Dr	Derfel	ap Dafydd
Post	Consultant Radiologist		
Details of professional registration	(●) General Medical Council ( ) General Dental Council		
Registration no	6115296		
Organisation	The Royal Marsden NHS Foundation Trust		
Address	Fulham Road		
Post Code	SW3 6JJ		
Telephone	02073528171		
Fax			
Mobile			
Email	derfel.apdafydd@rmh.nhs.uk		

Employers responsible for radiation facilities at research sites must have written procedures to meet the requirements of the Ionising Radiation (Medical Exposure) Regulations 2000 (IRMER). R & D offices for NHS sites will seek confirmation from local radiation experts that local IRMER authorisation procedures have been followed. Where the local Medical Physics Expert or IRMER Practitioner disagrees with the assessments made in this Section and/or the care organisation is unable to adhere to the protocol, this should be discussed with the Chief Investigator and the lead experts for the study. Any necessary

variation in the protocol or participant information sheet at particular sites should be notified to the main REC as a substantial amendment and an ethical opinion sought.

Part B: Section 4 – Use of residual or existing stored human tissue(or other human biological materials)

1. What types of human tissue or other biological material will be included in the study?

All participants will have undergone a partial or total nephrectomy as part of current standard-of-care. Access to nephrectomy archival formalin fixed paraffin embedded (FFPE) tissue blocks (normal and tumour tissue) will be obtained from all study participants.

2. Will the samples be released to the researcher:

In fully anonymised form? *(link to stored tissue and data is broken)*
(●) Yes ( ) No

In linked anonymised form? *(linked to stored tissue but donor not identifiable to researchers)*
( ) Yes (●) No

In a form in which the donor could be identifiable to researchers?
( ) Yes (●) No

3. Has consent been obtained previously to use the samples for research

(●) Consent has been given for all samples
( ) Consent has been given for some of the samples
( ) No consent has been given

4. Please outline what consents are already in place, distinguishing between different groups of samples where appropriate.

Collection of FFPE blocks is a mandatory aspect of the study. All participants will be informed via the Patient Information Sheet and consent to obtain samples will be obtained prior to randomisation.

6. Will any tissues or cells be used for human application or to carry out testing for human application in this research?

( ) Yes (●) No

8. What types of test or analysis will be carried out on the samples?

Tissue samples will be tested for PD-L1 expression to assess if it predicts response to immune checkpoint inhibitors and become a marker for clinical benefit in adjuvant RCC.

9. Will the research involve the analysis or use of human DNA in the samples?

(●) Yes ( ) No

10. Is it possible that the research could produce findings of clinical significance for donors or their relatives?

( ) Yes (●) No

11. If so, will arrangements be made to notify the individuals concerned?

- ○ Yes
- ○ No
- ◉ Not applicable

12. Who is the holder of the samples?

Please tick either/both boxes as applicable.

- ☑ NHS pathology department(s) / diagnostic archive(s)
  Specific details of each department/archive are not required
- ☐ Other research tissue bank(s) or sample collection(s)
  Please provide further details of each bank/collection below

13. Will any of the samples be imported from outside the UK?

◉ Yes ○ No

If Yes, please give further details and justify the use of imported samples. Summarise what arrangements have been made, where appropriate, to seek consent from donors and ethical review in the exporting country.

Due to the international nature of the trial, participating centres will be in Australia, New Zealand, France and USA. Tissue blocks will be collected from participants at each international centre and sent to a central biobank in the UK in batches (Cambridge University Hospitals NHS Foundation Trust BioRepository).

The collection of samples will comply with legal, regulatory and ethical and IATA requirements in the exporting country. Delegated national coordinating centres will facilitate the regulatory and ethical submission of the protocol and all patient related documents in compliance with national regulations and guidelines on collecting human tissue.

14. Please give details of where the samples will be stored, who will have access and the custodial arrangements.

Tissue blocks will be initially collected as part of routine care post-surgery and stored at local hospital's pathology departments. Blocks will be retrieved from local centres and sent to Cambridge University Hospitals NHS Foundation Trust Bio-Repository for storage and analysis.

15. What will happen to the samples at the end of the research? *Please tick all that apply and give further details.*

- ☑ Return to current holder of the samples
- ☐ Transfer to another tissue bank

(If the bank is in England, Wales or Northern Ireland a licence from the Human Tissue Authority will be required to store relevant material for possible further research.)

- ☐ Storage by research team pending ethical approval for use in another project

(Unless the researcher's institution holds a storage licence from the Human Tissue Authority, or the tissue is stored in Scotland, or it is not relevant material, a further application for ethical review should be submitted before the end of this project.)

- ☐ Storage by research team as part of a new research tissue bank

(The institution will require a storage licence for research from the Human Tissue Authority if the bank will be storing relevant material in England, Wales or Northern Ireland. A separate application for ethical review of the tissue bank

may also be submitted.)

☐ Storage by research team of biological material which is not “relevant material” for the purposes of the Human Tissue Act

☐ Disposal in accordance with the Human Tissue Authority Code of Practice

☐ Other

☐ Not yet known

Please give further details of the proposed arrangements:

Unused samples will be repatriated to local NHS/national pathology departments

Part B: Section 5 – Use of newly obtained human tissue(or other human biological materials) for research purposes

1. What types of human tissue or other biological material will be included in the study?

One EDTA blood sample will be collected at baseline visit (pre-treatment) from each participant after consent has been obtained.

2. Who will collect the samples?

Samples will be collected by appropriately trained, local research teams using collection kits provided by the Sponsor.

3. Who will the samples be removed from?

- [x] Living donors
- [ ] The deceased

4. Will informed consent be obtained from living donors for use of the samples? *Please tick as appropriate*

In this research?

(●) Yes ( ) No

In future research?

(●) Yes ( ) No ( ) Not applicable

6. Will any tissues or cells be used for human application or to carry out testing for human application in this research?

( ) Yes (●) No

8. Will the samples be stored: *[Tick as appropriate]*

In fully anonymised form? *(link to donor broken)*

(●) Yes ( ) No

In linked anonymised form? *(linked to stored tissue but donor not identifiable to researchers)*

( ) Yes (●) No

In a form in which the donor could be identifiable to researchers?

( ) Yes (●) No

9. What types of test or analysis will be carried out on the samples?

Immune-based molecular profiles (including inhibitory (e.g. Lag3) and agonist (e.g. OXO40) receptors as well as antigen presenting molecules will be identified in tumour tissue of patients with localised RCC to predict outcomes to adjuvant immunotherapy.

Single nucleotide polymorphisms will be assessed to establish auto-immune related genes can predict

immunotoxicity.

Cytokine and PBMC signatures can be identified in plasma to predict favourable outcomes to adjuvant treatment with immunotherapy as well as response to single vs combination immunotherapy.

10. Will the research involve the analysis or use of human DNA in the samples?

(●) Yes ( ) No

11. Is it possible that the research could produce findings of clinical significance for donors or their relatives?

( ) Yes (●) No

12. If so, will arrangements be made to notify the individuals concerned?

( ) Yes ( ) No (●) Not applicable

13. Give details of where the samples will be stored, who will have access and the custodial arrangements.

Baseline blood samples will be collected by participating centres and sent securely to Academic Urology Group (Cambridge) to be processed for analysis.

14. What will happen to the samples at the end of the research? *Please tick all that apply and give further details.*

☐ Transfer to research tissue bank

(If the bank is in England, Wales or Northern Ireland the institution will require a licence from the Human Tissue Authority to store relevant material for possible further research.)

☐ Storage by research team pending ethical approval for use in another project

(Unless the researcher's institution holds a storage licence from the Human Tissue Authority, or the tissue is stored in Scotland, or it is not relevant material, a further application for ethical review should be submitted before the end of this project.)

☐ Storage by research team as part of a new research tissue bank

(The institution will require a licence from the Human Tissue Authority if the bank will be storing relevant material in England, Wales or Northern Ireland. A separate application for ethical review of the tissue bank may also be submitted.)

☐ Storage by research team of biological material which is not "relevant material" for the purposes of the Human Tissue Act

☑ Disposal in accordance with the Human Tissue Authority's Code of Practice

☐ Other

☐ Not yet known

Please give further details of the proposed arrangements:

PART C: Overview of research sites

Please enter details of the host organisations (Local Authority, NHS or other) in the UK that will be responsible for the research sites. *For further information please refer to guidance.*

Investigator identifier	Research site		Investigator Name	
IN1	◉ NHS site ○ Non-NHS site		Forename	Gordon
			Middle name	
			Family name	Urquhart
	Country: Scotland		Email	gurquhart@nhs.net
			Qualification (MD...)	MB ChB, MRCP
			Country	UNITED KINGDOM
	Institution name	ABERDEEN ROYAL INFIRMARY		
	Department name			
	Street address			
	Town/city			
	Post Code			
IN2	◉ NHS site ○ Non-NHS site		Forename	Sarah
			Middle name	
			Family name	Welsh
	Country: England		Email	Sarah.welsh@addenbrookes.nhs.uk
			Qualification (MD...)	BSc, PhD, BMChB, MRCP
			Country	UNITED KINGDOM
	Organisation name	CAMBRIDGE UNIVERSITY HOSPITALS NHS FOUNDATION TRUST		
	Address	ADDENBROOKES HOSPITAL		
		HILLS ROAD		
		CAMBRIDGE CAMBRIDGESHIRE		
	Post Code	CB2 0QQ		
IN3	◉ NHS site ○ Non-NHS site		Forename	Balaji
			Middle name	
			Family name	Venugopal
	Country: Scotland		Email	balajivenugopal@nhs.net
			Qualification (MD...)	MBBC, MD, MRCP, FRCP

	Institution name	BEATSON WEST OF SCOTLAND CANCER CENTRE	Country	UNITED KINGDOM
	Department name			
	Street address			
	Town/city	GLASGOW		
	Post Code			

IN4

- (●) NHS site
- ( ) Non-NHS site

Country: England

Organisation name	UNIVERSITY HOSPITALS BRISTOL NHS FOUNDATION TRUST	Forename	Amit
Address	MARLBOROUGH STREET	Middle name	
	BRISTOL AVON	Family name	Bahl
Post Code	BS1 3NU	Email	amitbahl@doctors.org.uk
		Qualification (MD...)	
		Country	UNITED KINGDOM

IN5

- (●) NHS site
- ( ) Non-NHS site

Country: England

Organisation name	MID ESSEX HOSPITAL SERVICES NHS TRUST	Forename	Gopalakrishnan
Address	BROOMFIELD HOSPITAL	Middle name	
	COURT ROAD	Family name	Srinivasan
	CHELMSFORD ESSEX	Email	gopalakrishnan.srinivasan@meht.nhs.uk
Post Code	CM1 7ET	Qualification (MD...)	MBBS, PLAB, MD, MRCP
		Country	UNITED KINGDOM

IN6

- (●) NHS site
- ( ) Non-NHS site

Country: England

		Forename	David
		Middle name	
		Family name	Farrugia
		Email	david.farrugia@glos.nhs.uk
		Qualification (MD...)	

			Country	UNITED KINGDOM
	Organisation name	GLOUCESTERSHIRE HOSPITALS NHS FOUNDATION TRUST		
	Address	TRUST HQ 1 COLLEGE LAWN CHELTENHAM GLOUCESTERSHIRE		
	Post Code	GL53 7AG		

IN7

(●) NHS site
( ) Non-NHS site

Country: England

			Forename	Andrew
			Middle name	
			Family name	Protheroe
			Email	Andrew.protheroe@oncology.ox.ac.uk
			Qualification (MD...)	MMBS, PhD, FRCP
			Country	UNITED KINGDOM
	Organisation name	OXFORD UNIVERSITY HOSPITALS NHS FOUNDATION TRUST		
	Address	JOHN RADCLIFFE HOSPITAL HEADLEY WAY HEADINGTON OXFORD OXFORDSHIRE		
	Post Code	OX3 9DU		

IN8

(●) NHS site
( ) Non-NHS site

Country: England

			Forename	Dakshinamoorthy
			Middle name	
			Family name	Muthukumar
			Email	muthu.kumar@colchesterhospital.nhs.uk
			Qualification (MD...)	FRCR, MSc, MRCP, MD, MBBS
			Country	UNITED KINGDOM
	Organisation name	COLCHESTER HOSPITAL UNIVERSITY NHS FOUNDATION TRUST		
	Address	COLCHESTER DISTRICT GENERAL HO TURNER ROAD COLCHESTER ESSEX		
	Post Code	CO4 5JL		

IN9

◉ NHS site
○ Non-NHS site

Country: England

Organisation name	THE CLATTERBRIDGE CANCER CENTRE NHS FOUNDATION TRUST
Address	CLATTERBRIDGE ROAD BEBINGTON WIRRAL MERSEYSIDE
Post Code	CH63 4JY

Forename	Richard
Middle name	
Family name	Griffiths
Email	richard.griffiths1@nhs.net
Qualification (MD...)	BSc, MB ChB, PhD, MRCP
Country	UNITED KINGDOM

IN10

◉ NHS site
○ Non-NHS site

Country: England

Organisation name	PLYMOUTH HOSPITALS NHS TRUST
Address	DERRIFORD HOSPITAL DERRIFORD ROAD PLYMOUTH DEVON
Post Code	PL6 8DH

Forename	Saed
Middle name	
Family name	Hussain
Email	
Qualification (MD...)	
Country	UNITED KINGDOM

IN11

◉ NHS site
○ Non-NHS site

Country: England

Organisation name	NORTHERN LINCOLNSHIRE AND GOOLE NHS FOUNDATION TRUST
Address	DIANA PRINCESS OF WALES HOSPITAL SCARTHO ROAD GRIMSBY SOUTH HUMBERSIDE
Post Code	DN33 2BA

Forename	Iqtedar
Middle name	
Family name	Muazzam
Email	Iqtedar.muazzam@hey.nhs.uk
Qualification (MD...)	MBBS,FCPS
Country	UNITED KINGDOM

IN12

- (●) NHS site
- ( ) Non-NHS site

Country: England

Organisation name	THE NEWCASTLE UPON TYNE HOSPITALS NHS FOUNDATION TRUST
Address	FREEMAN HOSPITAL FREEMAN ROAD HIGH HEATON NEWCASTLE-UPON-TYNE TYNE AND WEAR
Post Code	NE7 7DN

Forename	Rhona
Middle name	
Family name	McMenemin
Email	rhona.mcmenemin@nuth.nhs.uk
Qualification (MD...)	FRCP, FRCR, FRCPI, MRCPI, MSc, MBChB
Country	UNITED KINGDOM

IN13

- (●) NHS site
- ( ) Non-NHS site

Country: Wales

Institution name	Glan Clwyd Hospital
Department name	
Street address	
Town/city	Rhyl
Post Code	LL18 5UJ

Forename	Carey
Middle name	
Family name	MacDonald Smith
Email	carey.macdonald-smith@wales.nhs.uk
Qualification (MD...)	MB BCH, MRCP, PGCert
Country	UNITED KINGDOM

IN14

- (●) NHS site
- ( ) Non-NHS site

Country: England

Organisation name	HEART OF ENGLAND NHS FOUNDATION TRUST
Address	BIRMINGHAM HEARTLANDS HOSPITAL BORDESLEY GREEN EAST BIRMINGHAM WEST MIDLANDS

Forename	Daniel
Middle name	
Family name	Ford
Email	Daniel.Ford@uhb.nhs.uk
Qualification (MD...)	
Country	UNITED KINGDOM

Post Code B9 5ST

IN15

◉ NHS site
○ Non-NHS site

Country: England

Organisation name: GUY'S AND ST THOMAS' NHS FOUNDATION TRUST
Address: TRUST OFFICES
GUY'S HOSPITAL
GREAT MAZE POND
LONDON GREATER LONDON
Post Code: SE1 9RT

Forename: Sarah
Middle name:
Family name: Rudman
Email: Sarah.rudman@gstt.nhs.uk
Qualification (MD...): BSc, PhD, MBBS, MRCP
Country: UNITED KINGDOM

IN16

◉ NHS site
○ Non-NHS site

Country: England

Organisation name: IPSWICH HOSPITAL NHS TRUST
Address: HEATH ROAD
IPSWICH SUFFOLK
Post Code: IP4 5PD

Forename: Ramachandran
Middle name:
Family name: Venkitaraman
Email: ramachandran.venkitaraman@nhs.net
Qualification (MD...): MBBS MD MRCP FRCR
Country: UNITED KINGDOM

IN17

◉ NHS site
○ Non-NHS site

Country: England

Organisation name: SOUTH TEES HOSPITALS NHS FOUNDATION TRUST
Address: JAMES COOK UNIVERSITY HOSPITAL

Forename: Alison
Middle name:
Family name: Humphreys
Email: alison.humphreys@stees.nhs.uk
Qualification (MD...):
Country: UNITED KINGDOM

	MARTON ROAD	
	MIDDLESBROUGH	
	CLEVELAND	
Post Code	TS4 3BW	

IN18

- (●) NHS site
- ( ) Non-NHS site

Country: England

Organisation name	UNIVERSITY HOSPITALS OF LEICESTER NHS TRUST
Address	GWENDOLEN HOUSE
	GWENDOLEN ROAD
	LEICESTER
	LEICESTERSHIRE
Post Code	LE5 4QF

Forename	Guy
Middle name	
Family name	Faust
Email	Guy.faust@uhl-tr.nhs.uk
Qualification (MD...)	MBBS, BSc, MRCP
Country	UNITED KINGDOM

IN19

- (●) NHS site
- ( ) Non-NHS site

Country: England

Organisation name	MAIDSTONE AND TUNBRIDGE WELLS NHS TRUST
Address	MAIDSTONE HOSPITAL
	HERMITAGE LANE
	MAIDSTONE KENT
Post Code	ME16 9QQ

Forename	Sharon
Middle name	
Family name	Beesley
Email	sbeesley@nhs.net
Qualification (MD...)	
Country	UNITED KINGDOM

IN20

- (●) NHS site
- ( ) Non-NHS site

Country: England

Forename	Paul
Middle name	
Family name	Nathan
Email	p.nathan@nhs.net
Qualification (MD...)	MBBS, PhD, FRCP

			Country	UNITED KINGDOM
	Organisation name	EAST AND NORTH HERTFORDSHIRE NHS TRUST		
	Address	LISTER HOSPITAL COREYS MILL LANE STEVENAGE HERTFORDSHIRE		
	Post Code	SG1 4AB		

IN21

(●) NHS site
( ) Non-NHS site

Country: England

		Forename	John
		Middle name	
		Family name	Graham
		Email	John.graham@tst.nhs.uk
		Qualification (MD...)	BSc, MB, ChB, MRCP, FRCP
		Country	UNITED KINGDOM
	Organisation name	TAUNTON AND SOMERSET NHS FOUNDATION TRUST	
	Address	MUSGROVE PARK HOSPITAL TAUNTON SOMERSET	
	Post Code	TA1 5DA	

IN22

(●) NHS site
( ) Non-NHS site

Country: England

		Forename	Gaurav
		Middle name	
		Family name	Kapur
		Email	gaurav.kapur@nnuh.nhs.uk
		Qualification (MD...)	
		Country	UNITED KINGDOM
	Organisation name	NORFOLK AND NORWICH UNIVERSITY HOSPITALS NHS FOUNDATION TRUST	
	Address	COLNEY LANE COLNEY NORWICH NORFOLK	
	Post Code	NR4 7UY	

IN23

(●) NHS site
( ) Non-NHS site

		Forename	Poulam
		Middle name	

Country: England

Family name	Patel
Email	poulam.patel@nottingham.ac.uk
Qualification (MD...)	FRCP, JCHMT, PhD, MRCP, MBBS
Country	UNITED KINGDOM

Organisation name	NOTTINGHAM UNIVERSITY HOSPITALS NHS TRUST
Address	TRUST HEADQUARTERS QUEENS MEDICAL CENTRE DERBY ROAD NOTTINGHAM NOTTINGHAMSHIRE
Post Code	NG7 2UH

IN24

(●) NHS site
( ) Non-NHS site

Country: England

Forename	Joanna
Middle name	
Family name	Gale
Email	joanna.gale@porthosp.nhs.uk
Qualification (MD...)	MD, FRCO, MRCP, BM
Country	UNITED KINGDOM

Organisation name	PORTSMOUTH HOSPITALS NHS TRUST
Address	DE LA COURT HOUSE QUEEN ALEXANDRA HOSPITAL SOUTHWICK HILL ROAD PORTSMOUTH HAMPSHIRE
Post Code	PO6 3LY

IN25

(●) NHS site
( ) Non-NHS site

Country: England

Forename	Emilio
Middle name	
Family name	Porfiri
Email	emilio.porfiri@uhb.nhs.uk
Qualification (MD...)	
Country	UNITED KINGDOM

Organisation name	UNIVERSITY HOSPITALS BIRMINGHAM NHS FOUNDATION TRUST
Address	TRUST HQ, PO BOX 9551 QUEEN ELIZABETH MEDICAL CENTRE EDGBASTON

	BIRMINGHAM WEST MIDLANDS
Post Code	B15 2TH

IN26

- (●) NHS site
- ( ) Non-NHS site

Country: Scotland

Institution name	Raigmore Hospital, NHS Highland
Department name	
Street address	
Town/city	Inverness
Post Code	IV2 3UJ

Forename	Neil
Middle name	
Family name	McPhail
Email	Neil.mcphail@nhs.net
Qualification (MD...)	MB ChB, MRCP, FRCP
Country	UNITED KINGDOM

IN27

- (●) NHS site
- ( ) Non-NHS site

Country: England

Organisation name	ROYAL BERKSHIRE NHS FOUNDATION TRUST
Address	ROYAL BERKSHIRE HOSPITAL LONDON ROAD READING BERKSHIRE
Post Code	RG1 5AN

Forename	Helen
Middle name	
Family name	O'Donnell
Email	Helen.o'donnell@royalberkshire.nhs.uk
Qualification (MD...)	
Country	UNITED KINGDOM

IN28

- (●) NHS site
- ( ) Non-NHS site

Country: England

Organisation name	THE ROYAL BOURNEMOUTH AND CHRISTCHURCH HOSPITALS NHS FOUNDATION TRUST
Address	ROYAL BOURNEMOUTH GENERAL HOSPITAL

Forename	Tom
Middle name	
Family name	Geldart
Email	Tom.geldart@rbch.nhs.uk
Qualification (MD...)	FRCP, DM, CCST, MRCP, MBBS, BSc
Country	UNITED KINGDOM

		CASTLE LANE EAST BOURNEMOUTH DORSET
	Post Code	BH7 7DW

IN29

- (●) NHS site
- ( ) Non-NHS site

Country: England

Organisation name	DERBY TEACHING HOSPITALS NHS FOUNDATION TRUST
Address	ROYAL DERBY HOSPITAL UTTOXETER ROAD DERBY DERBYSHIRE
Post Code	DE22 3NE

Forename	Prabir
Middle name	
Family name	Chakraborti
Email	prabir.chakraborti1@nhs.net
Qualification (MD...)	
Country	UNITED KINGDOM

IN30

- (●) NHS site
- ( ) Non-NHS site

Country: England

Organisation name	ROYAL DEVON AND EXETER NHS FOUNDATION TRUST
Address	ROYAL DEVON & EXETER HOSPITAL BARRACK ROAD EXETER DEVON
Post Code	EX2 5DW

Forename	Denise
Middle name	
Family name	Sheehan
Email	denise.sheehan@nhs.net
Qualification (MD...)	MB, BCh, FRCR
Country	UNITED KINGDOM

IN31

- (●) NHS site
- ( ) Non-NHS site

Country: England

Forename	Ekaterini
Middle name	
Family name	Boleti
Email	ekaterini.boleti@nhs.net
Qualification (MD...)	MB, BCh, FRCR

			Country	UNITED KINGDOM
	Organisation name	ROYAL FREE LONDON NHS FOUNDATION TRUST		
	Address	ROYAL FREE HOSPITAL POND STREET LONDON GREATER LONDON		
	Post Code	NW3 2QG		

IN32

(●) NHS site
( ) Non-NHS site

Country: England

Forename	James		
Middle name			
Family name	Larkin		
Email	james.larkin@rmh.nhs.uk		
Qualification (MD...)	PhD FRCP		
Country	UNITED KINGDOM		
Organisation name	THE ROYAL MARSDEN NHS FOUNDATION TRUST		
Address	FULHAM ROAD LONDON GREATER LONDON		
Post Code	SW3 6JJ		

IN33

(●) NHS site
( ) Non-NHS site

Country: England

Forename	Natalie		
Middle name			
Family name	Charnley		
Email	Natalie.charnley@lthtr.nhs.uk		
Qualification (MD...)	BSc, MBChB, FRCP		
Country	UNITED KINGDOM		
Organisation name	LANCASHIRE TEACHING HOSPITALS NHS FOUNDATION TRUST		
Address	CHIEF EXECUTIVE'S OFFICE ROYAL PRESTON HOSPITAL SHAROE GREEN LANE, FULWOOD PRESTON LANCASHIRE		
Post Code	PR2 9HT		

IN34

◉ NHS site
○ Non-NHS site

Country: England

Organisation name	UNIVERSITY HOSPITALS OF NORTH MIDLANDS NHS TRUST
Address	NEWCASTLE ROAD
	STOKE-ON-TRENT
	STAFFORDSHIRE
Post Code	ST4 6QG

Forename	Salil
Middle name	Vengalil
Family name	
Email	Salil.Vengalil@uhnm.nhs.uk
Qualification (MD...)	FRCR, MRCP, MBBS
Country	UNITED KINGDOM

IN35

◉ NHS site
○ Non-NHS site

Country: England

Organisation name	SALISBURY NHS FOUNDATION TRUST
Address	SALISBURY DISTRICT HOSPITAL
	ODSTOCK ROAD
	SALISBURY WILTSHIRE
Post Code	SP2 8BJ

Forename	Adi
Middle name	
Family name	Bhatnagar
Email	Adityanarayan.Bhatnagar@salisbury.nhs.uk
Qualification (MD...)	MBBS, MD CCST
Country	UNITED KINGDOM

IN36

◉ NHS site
○ Non-NHS site

Country: England

Organisation name	NORTHERN LINCOLNSHIRE AND GOOLE NHS FOUNDATION TRUST
Address	DIANA PRINCESS OF WALES HOSPITAL
	SCARTHO ROAD
	GRIMSBY SOUTH HUMBERSIDE

Forename	Sanjay
Middle name	
Family name	Dixit
Email	Sanjay.dixit@hey.nhs.uk
Qualification (MD...)	MBBS, MD, FRCR
Country	UNITED KINGDOM

Post Code DN33 2BA

IN37

◉ NHS site
○ Non-NHS site

Country: England

Organisation name: SOUTH TYNESIDE NHS FOUNDATION TRUST
Address: SOUTH TYNESIDE DISTRICT HOSPITAL, HARTON LANE, SOUTH SHIELDS TYNE AND WEAR
Post Code: NE34 0PL

Forename: Ashraf
Middle name:
Family name: Azzabi
Email: ashraf.azzabi@nuth.nhs.uk
Qualification (MD...): MD, MBBCh
Country: UNITED KINGDOM

IN38

◉ NHS site
○ Non-NHS site

Country: England

Organisation name: SOUTHEND UNIVERSITY HOSPITAL NHS FOUNDATION TRUST
Address: PRITTLEWELL CHASE, WESTCLIFF-ON-SEA ESSEX
Post Code: SS0 0RY

Forename: Awais
Middle name:
Family name: Jalil
Email: awais.jalil@nhs.net
Qualification (MD...):
Country: UNITED KINGDOM

IN39

◉ NHS site
○ Non-NHS site

Country: England

Organisation name: BARTS HEALTH NHS TRUST
Address: THE ROYAL LONDON HOSPITAL

Forename: Thomas
Middle name:
Family name: Powles
Email: thomas.powles@bartshealth.nhs.uk
Qualification (MD...): MBBS, MRCP, MD
Country: UNITED KINGDOM

	WHITECHAPEL
	LONDON GREATER LONDON
Post Code	E1 1BB

IN40

- (●) NHS site
- ( ) Non-NHS site

Country: England

Organisation name	LEEDS TEACHING HOSPITALS NHS TRUST
Address	ST. JAMES'S UNIVERSITY HOSPITAL
	BECKETT STREET
	LEEDS WEST YORKSHIRE
Post Code	LS9 7TF

Forename	Naveen
Middle name	
Family name	Vasudev
Email	n.vasudev@nhs.net
Qualification (MD...)	MBChB, MRCP, PhD ,BMSc
Country	UNITED KINGDOM

IN41

- (●) NHS site
- ( ) Non-NHS site

Country: England

Organisation name	CITY HOSPITALS SUNDERLAND NHS FOUNDATION TRUST
Address	SUNDERLAND ROYAL HOSPITAL
	KAYLL ROAD
	SUNDERLAND TYNE AND WEAR
Post Code	SR4 7TP

Forename	Ashraf
Middle name	
Family name	Azzabi
Email	ashraf.azzabi@nuth.nhs.uk
Qualification (MD...)	MD, MBBCh
Country	UNITED KINGDOM

IN42

- (●) NHS site
- ( ) Non-NHS site

Country: England

Forename	Tom
Middle name	
Family name	Waddell
Email	Tom.Waddell@christie.nhs.uk
Qualification (MD...)	MBChB, MRCP, MD

	Organisation name	THE CHRISTIE NHS FOUNDATION TRUST	Country	UNITED KINGDOM
	Address	550 WILMSLOW ROAD WITHINGTON MANCHESTER GREATER MANCHESTER		
	Post Code	M20 4BX		

IN43

(●) NHS site
( ) Non-NHS site

Country: England

Organisation name	TORBAY AND SOUTH DEVON NHS FOUNDATION TRUST	Forename	Jorg
Address	HENGRAVE HOUSE TORBAY HOSPITAL NEWTON ROAD TORQUAY DEVON	Middle name	
		Family name	Michels
		Email	jorg.michels@nhs.net
		Qualification (MD...)	MD, PhD, MRCP
Post Code	TQ2 7AA	Country	UNITED KINGDOM

IN44

(●) NHS site
( ) Non-NHS site

Country: Wales

Institution name	Velindre Cancer Centre	Forename	Jim
Department name	Velindre NHS Trust	Middle name	
Street address		Family name	Barber
Town/city		Email	Jim.Barber@wales.nhs.uk
Post Code		Qualification (MD...)	MRCP, FRCP, MBBS
		Country	UNITED KINGDOM

IN45

(●) NHS site
( ) Non-NHS site

Country: England

		Forename	Janet
		Middle name	
		Family name	Brown
		Email	j.e.brown@sheffield.ac.uk
		Qualification (MD...)	MBBS, BSc, FRCP, MD

			Country	UNITED KINGDOM
	Organisation name	SHEFFIELD TEACHING HOSPITALS NHS FOUNDATION TRUST		
	Address	NORTHERN GENERAL HOSPITAL HERRIES ROAD SHEFFIELD SOUTH YORKSHIRE		
	Post Code	S5 7AU		

IN46

(●) NHS site
( ) Non-NHS site

Country: Wales

		Forename	Pasquale
		Middle name	
		Family name	Innominato
		Email	Pasquale.Innominato@wales.nhs.uk
		Qualification (MD...)	MD, PhD
		Country	UNITED KINGDOM
	Institution name	Ysbyty Gwynedd/Bangor Hospital	
	Department name		
	Street address		
	Town/city		
	Post Code		

IN47

(●) NHS site
( ) Non-NHS site

Country: England

		Forename	Anthony
		Middle name	
		Family name	Maraveyas
		Email	anthony.maraveyas@hey.nhs.uk
		Qualification (MD...)	MD, PhD, MRCP, FRCP
		Country	UNITED KINGDOM
	Organisation name	HULL AND EAST YORKSHIRE HOSPITALS NHS TRUST	
	Address	HULL ROYAL INFIRMARY ANLABY ROAD HULL NORTH HUMBERSIDE	
	Post Code	HU3 2JZ	

PART D: Declarations

D1. Declaration by Chief Investigator

1. The information in this form is accurate to the best of my knowledge and belief and I take full responsibility for it.

2. I undertake to abide by the ethical principles underlying the Declaration of Helsinki and good practice guidelines on the proper conduct of research.

3. If the research is approved I undertake to adhere to the study protocol, the terms of the full application as approved and any conditions set out by review bodies in giving approval.

4. I undertake to notify review bodies of substantial amendments to the protocol or the terms of the approved application, and to seek a favourable opinion from the main REC before implementing the amendment.

5. I undertake to submit annual progress reports setting out the progress of the research, as required by review bodies.

6. I am aware of my responsibility to be up to date and comply with the requirements of the law and relevant guidelines relating to security and confidentiality of patient or other personal data, including the need to register when necessary with the appropriate Data Protection Officer. I understand that I am not permitted to disclose identifiable data to third parties unless the disclosure has the consent of the data subject or, in the case of patient data in England and Wales, the disclosure is covered by the terms of an approval under Section 251 of the NHS Act 2006.

7. I understand that research records/data may be subject to inspection by review bodies for audit purposes if required.

8. I understand that any personal data in this application will be held by review bodies and their operational managers and that this will be managed according to the principles established in the Data Protection Act 1998.

9. I understand that the information contained in this application, any supporting documentation and all correspondence with review bodies or their operational managers relating to the application:

    - Will be held by the REC (where applicable) until at least 3 years after the end of the study; and by NHS R&D offices (where the research requires NHS management permission) in accordance with the NHS Code of Practice on Records Management.
    - May be disclosed to the operational managers of review bodies, or the appointing authority for the REC (where applicable), in order to check that the application has been processed correctly or to investigate any complaint.
    - May be seen by auditors appointed to undertake accreditation of RECs (where applicable).
    - Will be subject to the provisions of the Freedom of Information Acts and may be disclosed in response to requests made under the Acts except where statutory exemptions apply.
    - May be sent by email to REC members.

10. I understand that information relating to this research, including the contact details on this application, may be held on national research information systems, and that this will be managed according to the principles established in the Data Protection Act 1998.

11. I understand that the main REC or its operational managers may share information in this application or supporting documentation with the Medicines and Healthcare products Regulatory Agency (MHRA) where it is relevant to the Agency's statutory responsibilities.

12. Where the research is reviewed by a REC within the UK Health Departments Research Ethics Service, I understand that the summary of this study will be published on the website of the National Research Ethics Service (NRES), together with the contact point for enquiries named below. Publication will take place no earlier than 3 months after issue of the ethics committee's final opinion or the withdrawal of the application.

Contact point for publication*(Not applicable for R&D Forms)*

NRES would like to include a contact point with the published summary of the study for those wishing to seek further information. We would be grateful if you would indicate one of the contact points below.

- ◯ Chief Investigator
- ◯ Sponsor
- ◯ Study co-ordinator
- ◯ Student
- ◯ Other – please give details
- ◯ None

Access to application for training purposes *(Not applicable for R&D Forms)*

Optional – please tick as appropriate:

☐ I would be content for members of other RECs to have access to the information in the application in confidence for training purposes. All personal identifiers and references to sponsors, funders and research units would be removed.

This section was signed electronically by Dr James Larkin on 06/10/2017 10:59.

Job Title/Post:	Consultant Clinical Oncologist
Organisation:	The Royal Marsden NHS Foundation Trust
Email:	James.Larkin@rmh.nhs.uk

D2. Declaration by the sponsor's representative

If there is more than one sponsor, this declaration should be signed on behalf of the co−sponsors by a representative of the lead sponsor named at A64-1.

I confirm that:

1. This research proposal has been discussed with the Chief Investigator and agreement in principle to sponsor the research is in place.

2. An appropriate process of scientific critique has demonstrated that this research proposal is worthwhile and of high scientific quality.

3. Any necessary indemnity or insurance arrangements, as described in question A76, will be in place before this research starts. Insurance or indemnity policies will be renewed for the duration of the study where necessary.

4. Arrangements will be in place before the study starts for the research team to access resources and support to deliver the research as proposed.

5. Arrangements to allocate responsibilities for the management, monitoring and reporting of the research will be in place before the research starts.

6. The duties of sponsors set out in the Research Governance Framework for Health and Social Care will be undertaken in relation to this research.

7. The statutory responsibilities of sponsors set out in the Medicines for Human Use (Clinical Trials) Regulations 2004 will be undertaken in relation to this trial.

   Please note: *The declarations below do not form part of the application for approval above. They will not be considered by the Research Ethics Committee.*

8. Where the research is reviewed by a REC within the UK Health Departments Research Ethics Service, I understand that the summary of this study will be published on the website of the National Research Ethics Service (NRES), together with the contact point for enquiries named in this application. Publication will take place no earlier than 3 months after issue of the ethics committee's final opinion or the withdrawal of the application.

9. Specifically, for submissions to the Research Ethics Committees (RECs) I declare that any and all clinical trials approved by the HRA since 30th September 2013 (as defined on IRAS categories as clinical trials of medicines, devices, combination of medicines and devices or other clinical trials) have been registered on a publically accessible register in compliance with the HRA registration requirements for the UK, or that any deferral granted by the HRA still applies.

This section was signed electronically by Prof M Parmar on 06/10/2017 10:38.

Job Title/Post:

Organisation:

Email: