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)
ANIMATE

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)
- ☐ Her Majesty's Prison and Probation Service (HMPPS)
- ☑ Administration of Radioactive Substances Advisory Committee (ARSAC)

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

Department of Health

Administration of Radioactive Substances Advisory Committee (ARSAC)

Application for preliminary research assessment

Applications to ARSAC for individual research certificates at each site (i.e. research certificate application (RCA) forms) may not be submitted until this preliminary research assessment (PRA) form has been submitted. The first certificate application may be submitted alongside this form.

The majority of fields in this form are populated from the integrated dataset, however the fields in question 5 contain information about the Research Ethics Committee (REC) booked to review your application and so will only be populated once you have booked and submitted your application for ethical review. This means that if you choose to submit your application for ethical review after submitting this form these fields will remain blank.

Administrative information

1. Full title of study:

A phase II study of nivolumab monotherapy in patients with relapsed/refractory Hodgkin lymphoma, fit for autologous stem cell transplant, who fail to reach complete metabolic remission after first or second line salvage therapy

2. Details of Chief Investigator:

	Title	Forename/Initials	Surname
		Graham	Collins
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	Oxford		
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Mobile			
Email	graham.collins@ouh.nhs.uk		

3. Name of sponsor:

Name of organisation	University College London
Given name	Nick
Family name	McNally
Address	Joint Research Office, UCL, Gower Street
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Post code	WC1E 6BT
Country	UNITED KINGDOM
Telephone	020 7380 9995
Fax	020 7380 9937
E-mail	ctc.sponsor@ucl.ac.uk

4. Sponsor's contact point:

Title	Forename/Initials	Surname
Mr	Oliver	Schofield

Address	Haematology Trials Group. CR-UK & UCL Cancer Trials Centre
	90 Tottenham Court Road
	London
Post Code	W1T 4TJ
E-mail	ctc.animate@ucl.ac.uk
Telephone	02076799860
Fax	02076799861

5. Details of NHS Research Ethics Committee to which application for ethical review has been made:

Name of REC	London - South East
REC Reference Number	18/LO/0204
REC form submission date	11/01/2018
IRAS Project ID	216147

Overview of the research

6. Summary of the study:

The ANIMATE trial is testing a drug called Nivolumab in patients with Hodgkin lymphoma which has either relapsed after initial chemotherapy, or not responded well enough to initial chemotherapy. Usual treatment in this situation is 2-4 cycles of chemotherapy ('salvage treatment') followed by an autologous stem cell transplant (a transplant of the patient's own cells). The cure rate after a transplant is high if there has been a very good response to salvage treatment.

Response is assessed using PET-CT scans, where a small amount of radioactive glucose is injected and highlights areas where there is still active disease (a 'positive' PET scan). If the PET-CT scan is positive after salvage, more treatment is needed before transplant.

Nivolumab is a drug which targets cancer cells and recruits the immune system to fight the cells. Nivolumab is approved for use in a number of cancers, including in Hodgkin lymphoma patients who have relapsed after stem cell transplant. This trial tests whether nivolumab is effective if used earlier, before stem cell transplantation.

Patients will be registered to the trial during initial salvage treatment. After 2 cycles of combination chemotherapy (or 4 cycles if treated with brentuximab vedotin), patients will have a PET-CT scan, which will be reviewed by experts at St Thomas' Hospital, London. If the scan is negative, patients will not receive trial treatment and will be followed up only. If the scan is positive, patients who are fit for treatment will receive 4-8 cycles of nivolumab, given every 2 weeks. Response will be checked by PET-CT after 4 cycles. Patients with a negative scan or progressive disease will stop treatment. Patients with a positive scan will have 4 more cycles before a final PET-CT scan.

Patients on the trial will be followed up for at least 3 years.

7. Summary of main issues:

Cure rates with first line chemotherapy in Hodgkin lymphoma are now very good, so the patient population for this trial is relatively small. In order to maximise recruitment to the trial, the Trial Management Group agreed that patients should be identified and registered during first or second salvage treatment for Hodgkin lymphoma that is either refractory to initial treatment or in first relapse.

It is necessary to consent and recruit patients during their salvage therapy to allow for the post-salvage PET-CT scan, which is one of the key means of assessing eligibility for trial treatment, can be performed under trial-specific conditions and the images transferred to St Thomas' Hospital, London for expert central review.

Initially, eligibility for registration will be determined, based predominantly on medical history. Potentially suitable patients will be informed about the trial by a site investigator or delegated representative. A detailed Patient Information Sheet, which explains the trial in language understandable to a layperson, will be given to the patient. The patient will

be given adequate time to consider participation, and given the opportunity to ask questions. Experienced clinicians, the manufacturer of nivolumab, representatives of the PET reviewing team at St Thomas' Hospital and a patient representative have all reviewed and advised on the content of the Patient Information Sheet.

Detailed medical assessment of eligibility for trial treatment will be carried out after the centrally reviewed PET-CT scan has been performed. This is for two key reasons: (1) patients will continue to have salvage therapy after initial registration. The side-effects of salvage therapy may be cumulative, so it is important to wait for this treatment to be completed before assessing fitness for nivolumab; (2) 60-75% of patients are expected to have a negative PET-CT scan after initial salvage therapy. By delaying eligibility tests until the PET-CT scan has been reported, patients who have a negative scan, and therefore ineligible for trial treatment, can be spared trial-specific tests to assess fitness for nivolumab, some of which are not standard of care.

Patients who are ineligible for trial treatment, either by virtue of a negative PET-CT after initial salvage treatment, or because they are unfit to receive nivolumab, will be followed up for the purposes of the trial, and will receive further treatment for their lymphoma as directed by their treating clinician. All patients participating in the trial will receive active treatment for their lymphoma.

Nivolumab is provided free of charge for the trial by Bristol-Myers Squibb (BMS), who are also providing funding for management of the trial, laboratory work and reimbursement of part A research costs. BMS have committed to provide drug for the duration of the trial. Nivolumab is a Black Triangle product, requiring intensive safety monitoring. In addition to standard reporting of SUSARs to the REC and MHRA, and production of Development Safety Update Reports, anonymised SAE reports and pregnancy reports will be shared with BMS to allow for safety monitoring. Patients are informed of this in the Patient Information Sheet.

As with all cancer treatments, patients may experience side effects during treatment, which will be managed according to local policies. A treatment delay of up to 4 weeks between cycles is permitted if patients need time to recover from side-effects. Because it activates the immune system, nivolumab can cause autoimmune side-effects (where the immune system attacks non-cancerous tissue). Adverse events and serious adverse events (SAEs) will be reported during and after treatment. Anonymised copies of SAE reports will be sent to Bristol-Myers Squibb.

The known side effects of nivolumab will be discussed with the patient and clearly outlined in the Patient Information Sheet, including details of the main symptoms of autoimmune toxicities. Their GP will also be informed of these symptoms when they are sent the GP letter. Patients will have 24 hour per day access to medical advice and will be provided with a contact card and instructed to contact their clinical trial doctor urgently if they experience any new symptoms. If a patient is confirmed as having autoimmune toxicity due to nivolumab, UCL CTC will be notified via an SAE report. An anonymised copy of the report will be sent to Bristol-Myers Squibb.

A pregnancy risk assessment has been performed based on the information about use in pregnancy and breastfeeding contained within the summary of product characteristics for nivolumab. The risk to an unborn child is currently unknown. Women who are pregnant or breastfeeding will be excluded from taking part in the trial. A pregnancy test for women of child bearing potential will be required at screening. Pregnancy tests will also be performed prior to starting nivolumab, regularly throughout nivolumab treatment and monthly for 3 months after stopping nivolumab. Contraceptive guidance is also given in accordance with the manufacturer's guidelines. Female patients of childbearing potential must agree to use hormonal contraception during treatment and for 6 months afterwards. Male patients must use condoms and advise female partners of childbearing potential to use hormonal contraception throughout treatment and for 8 months afterwards. UCL CTC will be notified of any pregnancies occur during or after nivolumab. An anonymised copy of the report will be sent to Bristol-Myers Squibb. If the mother consents, UCL CTC will be provided with information about the outcome of the pregnancy, and this information will be shared with Bristol-Myers Squibb. If the mother does not consent to pregnancy follow up, no further information will be collected.

Patients will undergo up to three PET-CT scans for the purpose of the trial, two of which are in excess of standard care. Radiation protection experts have reviewed the trial and provided information on the associated risk in the Patient Information Sheet. PET-CT scans have to be carried out on approved scanners, under trial conditions. PET centres will be provided with an imaging manual specifying how scans are to be performed and sites will be provided with training. Patients may have to travel to a different hospital for their PET-CT scan, although efforts will be made to approve local scanners wherever possible. There is no funding available via the trial grant to refund travel expenses, however sites will receive a fixed payment for the scans in excess of standard care, and may elect to use some of this payment to refund travel expenses where appropriate.

Samples are collected for translational research associated with the trial; information about this is given to patients in the Patient Information Sheet. Formalin fixed paraffin embedded tumour blocks stored at site from a previous biopsy (either at relapse or initial diagnosis) will be sent to the Haematological Malignancy Diagnostic Service (HMDS) in Leeds for all patients following registration. A further two biopsy blocks may be collected in patients who have nivolumab treatment: (1) biopsy if the patient remains PET positive after 8 cycles of nivolumab (this is not standard

care, and is optional for the purpose of the trial - and the patient may still go on trial if they do not wish to have a repeat biopsy) (2) biopsy at relapse (if clinically indicated; standard care). Patients will be informed of this in the Patient Information Sheet. Patients will also be asked to consent for their samples to be stored at the HMDS for use in future research.

Up to 6 peripheral blood samples will be taken from patients who undergo nivolumab treatment, and sent to University College London Cancer Institute for biomarker analysis. Wherever possible, these will be taken at the time of routine blood samples, sparing patients additional visits.

The laboratory work and imaging review within the trial is being undertaken by recognised experts in the field.

A full risk assessment has been carried out for the trial by the Cancer Research UK & UCL Cancer Trials Centre (UCL CTC), who are managing the study, and a monitoring plan has been developed that is proportional to the level of risk involved in the trial. These will be kept under review regularly throughout the trial. All patients will also be covered under a UCL insurance policy for injury caused by their participation in the trial. NHS complaints mechanisms also apply.

All information collected will be kept strictly confidential. Scans and samples will be anonymised prior to sending to the relevant laboratories. Responsible individuals will view identifiable data only where this is relevant and necessary to the research. Patient consent will be obtained for this. Study patients will not be identifiable in published data. Data will be stored in a secure manner and this trial is registered with the Data Protection Officer at University College London in accordance with applicable Data Protection legislation.

Design and purpose of the research

8. Primary research question:

To assess whether nivolumab, given on its own, can be used effectively to treat patients with Hodgkin lymphoma that has either failed to respond to initial treatment or which has returned after initially responding to treatment, and has not responded fully to salvage chemotherapy. The trial aims to find out how many patients have a negative PET-CT scan after 4-8 cycles of nivolumab treatment.

9. Secondary research questions:

To investigate whether patients' disease relapses after nivolumab treatment, and if so, how long this takes to happen.

To find out how long patients live after nivolumab treatment.

To find out if patients who have a negative PET-CT scan after nivolumab take longer to relapse than those who have a positive PET-CT scan after nivolumab

To investigate what side effects patients experience from nivolumab treatment.

To find out whether it is safe for patients to have a stem cell transplant after nivolumab treatment

To investigate whether PET scanning is an effective way of checking response to nivolumab treatment

To look at whether there are blood tests that can be used to monitor response to treatment for Hodgkin lymphoma

To understand more about the biology of Hodgkin lymphoma, and whether it is possible to predict response to salvage treatment

10. Scientific background:

Hodgkin Lymphoma is one of the commonest cancers to affect the teenage and young adult age group. Although curable in around 80-85% of patients with first line treatment, those who relapse face more intensive treatments (called salvage treatments), followed by a potentially curative stem cell transplant. Patients who fail to achieve a very good remission prior to transplant tend to have a particularly poor outcome.

Currently, patients who fail to respond very well to first line salvage treatment face having further treatments which are either of limited efficacy (for example responses may not be achieved or may not last very long) or involve combination chemotherapy, with its associated risks and toxicities.

Nivolumab is a new drug in a class called PD1 inhibitors which increase the activity of the body's immune system to kill cancer cells. Nivolumab is currently licensed for patients with Hodgkin lymphoma who have relapsed after a stem cell transplant. In this patient population, nivolumab has shown excellent response rates and tends to be well tolerated.

The ANIMATE study is a phase II clinical trial assessing the effectiveness of nivolumab in patients who have failed to reach a very good remission with first or second line salvage treatment, in particular aiming to establish whether patients can be converted to PET-negativity before transplant, potentially increasing the chance of the transplant being successful.

Scientific studies will be carried out on tumour samples and blood samples from patients, aimed at working out who will do well with anti-PD1 treatment at this stage in their treatment, and learning more about how nivolumab works. The trial will also assess the value of PET scanning as a tool in assessing responses to nivolumab, and will explore alternative ways of measuring response by using changes in blood markers.

Applicants must enclose a copy of the completed request for authorisation from the Medicines and Healthcare products Regulatory Agency (MHRA). The application form is published as Annex 1 to the European Commission guideline ENTR/CT1 and can be obtained from the EudraCT website at http://eudract.emea.europa.eu.

11. Summary of the purpose, design and methodology of the research:

ANIMATE is a non-randomised, single arm trial assessing the efficacy of nivolumab in patients with primary refractory Hodgkin lymphoma or Hodgkin lymphoma in first relapse. Thirty patients will be treated on the trial.

While undergoing first or second line salvage therapy, patients with relapsed/refractory classical Hodgkin lymphoma will be approached, consented, and have an initial assessment of eligibility for trial. The initial assessment is based predominantly on the patient's medical history, although women of childbearing potential will also have a pregnancy test. If eligible, patients will be registered to the trial.

Following registration, a stored tumour biopsy sample will be sent to the central laboratory (Haematological Malignancy Diagnostic Service) for analysis. This will be retained if the patient consents to it being used in future research. If the hospital requests the block to be returned, or the patient does not consent for its use in future research, the block will be sent back to the hospital.

Patients will have a PET-CT scan after 2 cycles of salvage therapy (or 4 cycles if they are undergoing treatment with brentuximab vedotin). The scan will be reviewed by experts at St Thomas' Hospital, London to establish whether the patient is eligible for trial treatment.

Patients with a negative PET-CT scan (no evidence of active disease) will not be eligible for trial treatment. They will enter follow up for the trial and will receive further treatment for their lymphoma (probably a stem cell transplant) at their treating clinician's discretion. Approximately 60-75% are expected to have a negative PET-CT scan at this point.

Patients with a positive PET-CT scan (evidence of active disease) will be potentially eligible for trial treatment, and will have a full assessment of their fitness for treatment, including heart and lung function tests, a pregnancy test for women of childbearing potential, blood counts and blood chemistry testing. Some additional tests (including hepatitis testing and hormone levels) will be performed on routine blood samples. 25-40% are expected to have a positive PET-CT scan at this point.

Where tests show a patient is not fit for treatment, they will enter follow up for the trial and will have further treatment for their lymphoma at their treating clinician's discretion.

Eligible patients will have 4-8 cycles of nivolumab, which is given as an intravenous infusion in an outpatient setting every 2 weeks.

Before each cycle of nivolumab begins, patients will have a clinical examination, adverse event assessment and blood tests (full blood count, blood chemistry and tests for autoimmune conditions) to check that they are well enough to receive treatment. Blood oxygen levels will also be tested. Pregnancy tests (women of childbearing potential only) and thyroid function tests will be carried out periodically during treatment. Wherever possible these additional tests will be performed on routine blood samples.

Patients will have a PET-CT scan after 4 cycles. The scan images will be reviewed centrally at St Thomas' hospital, London. The result of this scan will determine what further treatment the patients receive:
- Patients with a negative PET-CT scan will stop trial treatment and enter follow up for the trial. Patients will also have a lung function test after stopping treatment. Further treatment for their lymphoma will be at their treating clinician's discretion.

- Patients who show progressive disease will stop trial treatment and enter follow up for the trial. Patients will also have a lung function test after stopping treatment. They will receive further treatment for their lymphoma at their treating clinician's discretion.
- Patients who are PET positive but with no evidence of disease progression will continue to have a further 4 cycles of nivolumab (total 8 cycles).

A final PET-CT scan will be performed after cycle 8, and reviewed centrally at St Thomas' Hospital, London. Patients who are PET positive at this point may have an optional biopsy at this point. The tumour block will be sent to the central laboratory (HMDS). Patients will also have a lung function test after completing treatment. They will receive further treatment for their lymphoma at their treating clinician's discretion.

Up to 6 blood samples will be collected from patients and sent to the central laboratory (UCL Cancer Institute). These will be taken at the beginning of cycles 1, 2, 4, 6 and 8 and after treatment. Wherever possible, the blood will be taken at the same time as routine blood tests to spare patients additional visits.

Patients will be followed up 1, 2, 3, 6, 9 and 12 months after stopping treatment and annually thereafter. Patients will have a clinical examination and blood tests at each follow up visit during the first year of follow up. Women of childbearing potential will have a pregnancy test 1, 2 and 3 months post treatment. Patients will have a lung function test a year after stopping trial treatment.

There are no protocol specified investigations at annual follow up visits, but the patient's remission status should be assessed and any late toxicity due to nivolumab much be reported.

If a patient relapses at any time, this will be reported to UCL CTC. If a biopsy is performed at the time of relapse, the tumour block should be sent to the central laboratory (HMDS, Leeds).

The trial will end when the final patient reaches 3 years of follow up.

12. 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
Tumour biopsy	0-2	0-1	45 mins	Surgical staff
Peripheral blood sample to be sent to central laboratory	6	0	5 mins	Nursing staff - in outpatient clinic.
Pregnancy test (Women of childbearing potential only)	9	0	5 mins	Nursing staff in outpatient clinic. N.B. the number of pregnancy tests a female patient would have as part of standard care would vary depending on the nature of the treatment they were receiving
Administration of intravenous chemotherapy (trial treatment)	8	0	60 mins	Nursing staff in outpatient day unit. Nivolumab is given as a 60 minute IV infusion once per cycle. The number of infusions a patient would have as part of standard care would vary depending on the nature of the treatment they were receiving.
PET-CT scan	1-3	1	2 hrs	Trained imaging healthcare professionals and medical staff in nuclear medicine department. Scans take 20-30 minutes and are performed after injection of tracer and a waiting period of 60 minutes to allow distribution of the tracer in the body, so

				patients spend up to 2 hours in the imaging department in total. The number of PET-CT scans a patient would receive as standard care would vary depending on the nature of the treatment they were receiving.
Clinical Examination	15	0	30 mins	Medical staff in outpatient clinic. N.B. The number of clinical examinations a patient would have as part of standard care would vary depending on the nature of the treatment they were receiving, but these are typically performed at each clinic in this patient population.
Weight	1	1	5 mins	Nursing staff in outpatient clinic. N.B. The number of weight measurements a patient would have off trial would vary depending on the treatment they were receiving.
Full blood count	15	0	5 mins	Nursing staff in outpatient clinic/local laboratory staff N.B. The number of tests a patient would have off trial would vary depending on the treatment they were receiving. FBCs are routinely carried out prior to each cycle of treatment and at follow up visits.
Biochemistry	15	0	5 mins	Nursing staff in outpatient clinic/local laboratory staff N.B. The number of tests a patient would have off trial would vary depending on the treatment they were receiving. Biochemistry tests are routinely carried out prior to each cycle of treatment and at follow up visits.
Tests for autoimmune conditions (N.B. additional tests performed on routine blood samples)	11	0	5 mins	Nursing staff in outpatient clinic/local laboratory staff N.B. The number of tests a patient would have off trial would vary depending on the treatment they were receiving. Tests for autoimmune conditions would likely be carried out only if clinically indicated in this population.
Echocardiogram	1	0	30 mins	Medical or nursing staff in outpatient clinic. Only performed if clinically indicated (e.g abnormalities on ECG)
Lung function test	3	0	60 mins	Medical or nursing staff in outpatient clinic
ECOG performance status assessment	1	0	5 mins	Medical staff in outpatient clinic (assessed based on clinical examination)
Hepatitis B & C serology (N.B. additional tests performed on routine blood samples)	1	0	5 mins	Nursing staff in outpatient clinic/local laboratory staff N.B. The number of tests a patient would have off trial would vary depending on the treatment they were receiving. Hepatitis testing would likely be carried out only if clinically indicated in this population.
Thyroid function test (N.B. additional tests performed on routine blood samples)	6	0	5 mins	Nursing staff. N.B. The number of tests a patient would have off trial would vary depending on the treatment they were receiving. Thyroid function tests would likely be carried out only if clinically indicated in this population.
ECG	1	0	5 mins	Nursing staff in outpatient clinic/local laboratory staff N.B. The number of tests a patient would have off trial would vary depending on the treatment they were receiving. An ECG would likely be carried out only if clinically indicated in this population.
Contrast Enhanced CT scan	1-3	0	30 mins	Trained imaging healthcare professionals and medical staff in local radiology department. To be performed at the same timepoints as PET-CT scans. May be part of the same visit if feasible. The number of CT scans a patient would receive as standard care would vary depending on the nature of the treatment they were receiving, and standard practice at their site.
Oxygen saturation test (pulse oximetry at rest)	8	0	5 mins	Nursing staff in outpatient clinic. N.B. The number of tests a patient would have off trial would vary depending on the treatment they were receiving.
Adverse event assessment	11	0	10 mins	Medical staff - carried out at routine assessments in clinic prior to each treatment cycle and follow up visits. N.B. The number of tests a patient would have off trial would vary depending on the treatment they were receiving.

13. Number of participants:

Total UK sample size:	120
Total international sample size (including UK):	120
Total in European Economic Area:	120

Further details:
The study will be conducted in the UK only.
120 to be registered, with an aim to treat 30 patients.

14. How was the number of participants decided upon?

Sample size was calculated using “Sample size tables for clinical studies” software.

Assuming that the overall response rate (ORR) will be around 60% (a conservative estimate based on ORRs of 65-87% seen in previous studies), but to rule out a rate <40% (i.e. BV given pre ASCT), using an A’hern design with 80% power and a one-sided alpha of 0.1 we require 30 patients. We hope to see at least 16 responses (CR or PR).

We assume that 25-40% of patient scans will be PET positive following first line salvage so in order to treat 30 patients we will need to register 75-120 patients. We will also replace any patient withdrawn before starting nivolumab or who is found to be ineligible after starting treatment. These patients will be excluded from all analyses of the nivolumab treated cohort (including the analysis of the primary endpoint), but will be included in analyses of the total cohort (i.e. all patients registered) if appropriate i.e. if the patients were eligible at this point.

Administration of radioactive materials

1. Does the study involve exposure to radioactive materials?

(●) Yes ( ) No

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

(●) Yes ( ) No

A. Radioactive materials

Details of radioactive materials

A1. Complete the table below for each radionuclide to be administered.

Type of investigation/therapy:	18F-FDG-PET/CT
Radionuclide:	18Fluorine
Chemical form:	fluorodeoxyglucose (FDG)
Proposed activity (MBq):	400MBq
Route of administration:	I.V.
Number of administrations per participant:	At least 1, up to 3
Effective dose or target tissue dose per administration:	7.6 mSv effective dose [ref. ARSAC Notes for tissue dose per Guidance 2016]

A2. Details of study participants

Will any of the study participants be patients? (●) Yes ( ) No

Will any of the study participants be healthy volunteers? ( ) Yes (●) No

Details of patients to be studied:

Number (whole study)	Age range	Sex	Clinical condition	Total effective or target tissue dose per individual
120	16+	M & F	Hodgkin lymphoma	94.8 mSv,

A3. What steps will you take to exclude women who are pregnant or who could become pregnant during the study? *Give details of screening procedures and advice to be given to women of child-bearing age.*

Pregnancy is an exclusion criterion for the trial. Women of childbearing age must have a pregnancy test as part of trial screening, and must consent to use effective contraception throughout treatment and for 6 months after trial treatment. Additional pregnancy testing will be undertaken prior to starting nivolumab, and every 4 weeks during trial treatment. However, it should be noted that the overall risk of pregnancy in this patient population (relapsed/refractory Hodgkin lymphoma, patients having recently undergone salvage chemotherapy) is considered to be low.

A4. ARSAC research certificates

An ARSAC research certificate will be required at each research site where the study involves administration of exposures which are additional to normal care. Most of the information required by ARSAC can be generated automatically from Part A and Part B Section 3 of IRAS once completed.

Administration of other ionising radiation

B1. Details of other ionising radiation

Procedure	No of procedures	Estimated procedure dose *(use national Diagnostic Reference Levels where available)*
PET-CT scan	Up to 3	The total dose received by patients in this study will be 94.8 mSv, from this total the 63.6 mSv is the additional dose received by participating in the study.
CT scan as part of PET/CT	Up to 3	8 mSv (protocol dependent)
Contrast enhanced CT scan	Up to 3	16 mSv

Dose and risk assessment

C1. What is the total research protocol dose from 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)?

STUDY TITLE
ANIMATE: A phase II study of nivolumab monotherapy in patients with relapsed/refractory Hodgkin lymphoma, fit for autologous stem cell transplant, who fail to reach complete metabolic remission after first or second line salvage therapy

INTRODUCTION
This is a single-arm, phase II, multi-centre study of the safety and efficacy of the PD-1 inhibitor, nivolumab, as second or third line salvage therapy as a bridge to stem cell transplant (SCT) in relapsed/ refractory classical Hodgkin lymphoma patients not achieving a complete metabolic response (cMR) on FDG-PET following initial salvage therapy. Up to 120 patients will be registered in the study in order to have 30 patients undergo treatment with nivolumab (assuming 25-40% will be PET positive after the first-line salvage chemotherapy).

Patients will have a half-body FDG-PET/CT scan as standard of care (SOC) practice to establish the presence of refractory disease or disease relapse following initial salvage chemotherapy.

Patients registered on the study will also have contrast enhanced CT (ceCT) before treatment with nivolumab as second or third salvage chemotherapy. An FDG-PET/CT scan and ceCT are then performed to assess treatment response after the first 4 cycles of second-line salvage chemotherapy (PET 4) and after a further 4 cycles (PET 8) in patients with a positive PET 4 scan.

DATA
All patients in the study will have at least two FDG-PET/CT scans as part of the study protocol. One after the 2nd cycle of first-line salvage treatment or after 4 cycles of brentuximab vedotin treatment to determine eligibility for second line salvage treatment with the study drug nivolumab. The second FDG-PET/CT scan will be performed after 4 cycles of nivolumab (PET 4). Patients with a positive PET 4 scan will receive a third FDG-PET/CT (PET 8) after 8 cycles of nivolumab.

Current practice would be to perform a FDG-PET/CT scan after the completion of first and second line salvage treatments to assess response and suitability for stem cell transplant. For patients who have 2 PET/CT scans both would therefore be considered part of normal care. For patients who have 3 scans, the additional scan to monitor response half way through nivolumab treatment would be additional to normal care.

Each PET part of the study consists of an injection of up to 400 MBq 18F-FDG PET tracer. This will give an effective dose of 7.6 mSv [1]. The suggested National Dose Reference Level (NDRL) for the CT portion of a half-body PET/CT examination is a dose length product (DLP) of 400mGy.cm and effective dose of 6.5mSv [2]. To make allowance for variations between sites, an upper effective dose of 8 mSv will be used to determine the dose constraint.

Up to 3 contrast enhanced chest-abdo-pelvis CT scans (ceCT) would be carried out during the study, following each PET/CT scan as part of the study protocol. Current practice does not involve ceCT in the management of these patients, so these scans are additional to SOC. The NDRL of 1000 mGycm [3] for a standard chest-abdo-pelvis scan gives rise to an effective dose of 16mSv.

The total dose received by patients in this study will be 94.8 mSv, from this total the 63.6 mSv is the additional dose received by participating in the study.

RISK ASSESSMENT
This study requires exposures to ionising radiation which are detailed in A1 and B1. Most of the total radiation dose required by the study is additional to routine clinical care. The total protocol dose is 63.6 mSv. This is equivalent to 29 years of average natural background radiation in the UK.

Ionising radiation can cause cancer which manifests itself after many years or decades. The risk of developing cancer as a consequence of taking part in this study is estimated as 0.4 %. For comparison, the natural lifetime cancer incidence in the general population is about 50%.

REFERENCES
1. ARSAC. Notes for Guidance on the Clinical Administration of Radiopharmaceuticals and Use of Sealed Radioactive Sources Administration of Radioactive Substances Advisory Committee. 2016.
2. Iball GR, Bebbington NA, Burniston M, Edyvean S, Fraser L, Julyan P, et al. A national survey of computed tomography doses in hybrid PET-CT and SPECT-CT examinations in the UK. 2017;
3. Shrimpton, PC, Hillier MC MS and GS. Public Health England - Doses from Computed Tomography (CT) Examinations in the UK – 2011 Review [Internet]. 2014. 1-129 p. Available from: https://www.gov.uk/government/uploads/system/uploads/attachment_d ata/file/349188/PHE_CRCE_013.pdf

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

This section was signed electronically by Ms Lucy Pike on 11/01/2018 12:00.

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C3. Details of person acting as lead Medical Physics Expert

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Clinical assessment

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

Currently PET/CT scans are part of normal care for assessing whether a patient has responded to salvage treatment for Hodgkin Lymphoma [1]. If a patient has responded well, this suggests a subsequent bone marrow transplant will have a high likelihood of achieving remission (cure). Usually PET/CT scans carried out at the end of a course of salvage treatment have the CT component performed at a low dose without contrast.

In this study, an additional PET/CT scan is performed to monitor the lymphoma during treatment with the study drug nivolumab. The extra scan is needed to determine if the patient is responding. If there is a complete metabolic response the patient may then consider to proceed to a bone marrow transplant at this time or if the disease has worsened to stop the study treatment and consider alternative therapies.

Contrast enhanced CT scans are performed in addition to PET/CT scans to assess anatomical response, as it is unclear that PET/CT (with low dose CT) will optimally assess response in all patients. This is because 'flare' responses with increased lesion size and FDG uptake have been reported in patients with other cancers receiving similar treatment.

Patients may benefit from taking part in the trial if the study drug increases their chances of achieving a remission. The trial will also help to determine how best to treat patients with Hodgkin Lymphoma who have relapsed or have disease that is resistant to treatment in the future.

The risks associated with the additional radiation burden are very low compared to the lifetime risk of developing cancer, and in particular for this group of patients who have lymphoma that is resistant to usual treatments.
The risks from the lymphoma and standard chemotherapy and radiotherapy that patients on study will have already received vastly outweigh any potential risk associated with this level of additional radiation.

REFERENCE
[1] Scarsbrook A and Barrington SF. Evidence based indications for the use of PET-CT in the United Kingdom 2016. Available from:
https://www.rcr.ac.uk/publication/evidence-based-indicatio ns-use-pet-ct-united-kingdom-2016
https://www.rcplondon.ac.uk/projects/outputs/evidence-based-ind ications-use-pet-ct-uk-2016

D3. Declaration by lead Clinical Radiation Expert

This section was signed electronically by Sally Barrington on 11/01/2018 12:05.

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D4. Details of lead Clinical Radiation Expert

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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.

Research sites

Investigator identifier	Research site		Investigator Name	
IN1	◉ NHS/HSC Site ○ Non-NHS/HSC Site		Forename Middle name Family name Email Qualification (MD...)	Graham Collins Graham.collins@ouh.nhs.uk MBBS, MRCP (UK), FRCPath, DPhil
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IN2

- (●) NHS/HSC Site
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IN3

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IN4

(●) NHS/HSC Site
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IN7

(●) NHS/HSC Site
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IN8

(●) NHS/HSC Site
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IN9

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IN10

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IN11

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IN12

◉ NHS/HSC Site
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IN13

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IN14

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IN15

◉ NHS/HSC Site
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IN16

◉ NHS/HSC Site
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IN17

◉ NHS/HSC Site
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IN18

◉ NHS/HSC Site
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Declaration by sponsor's representative

E1. Declaration

This declaration should be signed on behalf of the sponsor(s) by a duly authorised representative. This may be either an employee of the lead sponsor or a co-sponsor organisation, or a sub-contractor or any other person with delegated authority from the sponsor(s).

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

This section was signed electronically by Miss Nicole Gower on 07/03/2018 14:48.

Job Title/Post:	Regulatory manager
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For details of where to send your completed application, please refer to the submission tab for this form or the Contact Us page.