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

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)
ANIMATE

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

REC Name:
London - South East

REC Reference Number:
18/LO/0204

Submission date:
11/01/2018

PART A: Core study information

1. ADMINISTRATIVE DETAILS

A1. Full title of the research:

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

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

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

Given name	Graham
Family name	Collins
Qualification (MD...)	MBBS, DPhil, FRCPath
ORCID ID	
Institution name	Churchill Hospital
Institution department name	Department of Haematology
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Town/city	Oxford
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Work E-mail	graham.collins@ouh.nhs.uk
* Personal E-mail	
Work Telephone	01865235252
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Fax	

** 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
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

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:	UCL/15/0515
Protocol Version:	1.0
Protocol Date:	
Funder's reference number:	CA209-445
Project website:	

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):	
ClinicalTrials.gov Identifier (NCT number):	NCT03337919
European Clinical Trials Database (EudraCT) number:	2017-002544-32

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.*

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.

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.

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.

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)

Single arm, open label, multicentre phase II trial

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 exploratory trial (Phase II)

○ Therapeutic exploratory trial including comparison with the standard treatment regimen (Phase II/III)

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.*

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.

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

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

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

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.

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.*

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.

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
- [ ] 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 ANIMATE trial was developed by the Hodgkin lymphoma subgroup of the NCRI Lymphoma Clinical Studies Group (CSG), and has been reviewed and endorsed by the CSG. The membership of both the CSG and subgroup includes patient representatives, who have had input on the design of the trial and its acceptability to patients.

The Trial Management Group, who will oversee the trial, includes a patient representative. The patient representative has advised on the aspects of the trial protocol, in particular where there were questions about acceptability to patients, and has also reviewed and advised on the content of the Patient Information Sheet.

Patient support groups such as Cancerhelp and the Lymphoma Association will be involved in promoting the study and disseminating lay results when the trial ends.

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
- [ ] Renal and Urogenital
- [ ] Reproductive Health and Childbirth
- [ ] Respiratory
- [ ] Skin
- [ ] Stroke

Gender:	Male and female participants
Lower age limit: 16	Years
Upper age limit:	No upper age limit

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

Inclusion criteria for registration
• Age 16 or over
• Primary refractory classical Hodgkin lymphoma or classical Hodgkin lymphoma in first relapse
• About to receive, receiving or within 14 days of first 2 cycles of first or second line salvage therapy (4 cycles if receiving treatment with brentuximab vedotin)
• Fit for autologous stem cell transplantation
• Written informed consent
• Willing to comply with the contraceptive requirements of the trial

Inclusion criteria – trial treatment
• Has received 2 cycles of first line or second line salvage chemotherapy (4 cycles if being treated with brentuximab vedotin)
• PET positive (Deauville score 4 or 5) after 2 cycles of first or second line salvage chemotherapy (4 cycles if being treated with brentuximab vedotin)
• Fit for further salvage chemotherapy
• ECOG performance status 0-1
• Creatinine clearance >30ml/min calculated by Cockroft-Gault formula
• Bilirubin <1.5 x ULN, ALT/AST <2.5 x ULN
• Adequate bone marrow function (Hb >80g/l, Platelets >50 x 10^9/l, neutrophils >1.0 x 10^9/l

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

Exclusion criteria for registration
• Nodular lymphocyte predominant Hodgkin lymphoma
• Women who are pregnant or breastfeeding
• History of colitis, inflammatory bowel disease or pneumonitis
• Patients with autoimmune disorders excluding patients with vitiligo, diabetes mellitus type 1, hypo- and hyperthyroidism not requiring immunosuppressive therapy
• Known history of hepatitis B or C infection

• Known HIV infection
• History of allergy (including severe/life threatening skin reaction) to monoclonal antibodies, anaphylaxis or uncontrolled allergy
• Major surgery within 4 weeks prior to registration
• Myocardial infarction, unstable angina, coronary artery bypass graft, cerebrovascular accident or transient ischaemic attack within the past 6 months
• Non-haematological malignancy within the past 3 years (some exceptions apply – listed in trial protocol)

Exclusion criteria for trial treatment
• Deauville score 1-3 after 2 cycles of first or second line salvage chemotherapy (4 cycles if being treated with brentuximab vedotin)
• Positive serology for hepatitis B or C (unless due to vaccination)
• Active infection requiring systemic therapy
• Ongoing immunosuppressive therapy, apart from inhaled, intranasal, topical corticosteroids or systemic corticosteroids at low doses (≤10mg prednisolone or equivalent per day).
• Chemo- or radiotherapy or corticosteroids at a dose of more than 10mg/day prednisolone or equivalent within 14 days prior to response PET-CT. NOTE: corticosteroids can be used AFTER a positive PET-CT scan for symptomatic disease but must be weaned to a dose of prednisolone ≤10mg/day or less (or equivalent) at least 7 days prior to starting nivolumab.
• Treatment with any investigational agent within 28 days prior to planned start of nivolumab
• Ongoing grade 2-4 non-haematological toxicities related to prior Hodgkin lymphoma treatments, with the exception of alopecia and grade 2 fatigue
• Pregnant or breastfeeding women

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
Medical history check	2	0	30 mins	PI, co-investigator or other appropriately trained member of the local study team
Informed consent for trial	1	0	45 mins	PI, co-investigator or other appropriately trained member of the local study team

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
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.

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?

3-6 years.

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.

Patients will be treated by experienced staff at specialist Haematology/Oncology centres. In order to participate in the trial, principal investigators must confirm that they are experienced in treating patients with nivolumab or similar immune-oncology drugs.

The trial has a two-stage assessment of eligibility for trial treatment, in order to ensure that patients only undergo treatment with nivolumab if they are fit to do so. Screening investigations such as lung function tests, which are not standard of care in this patient population, will only be carried out once the post-initial salvage PET-CT scan has confirmed the patient is potentially eligible for trial treatment, in order to prevent patients undergoing non-standard tests unnecessarily.

Clinical teams will monitor patients closely for side effects, including regular blood tests to check blood cell counts and blood chemistry. Clinicians will give appropriate treatment to alleviate symptoms as necessary. Trial treatment can also be delayed for up to 4 weeks to allow patients to recover from side effects. The Patient Information Sheet outlines the known side effects of nivolumab and the symptoms of significant toxicities. Patients are provided with a patient card with a contact number on which they can seek medical advice or attention at any time, should the need arise. Patients' GPs will be informed that they are on a trial and what side effects are expected. GPs will also be informed about contraindicated concomitant medications.

There is no evidence available on the use of nivolumab during pregnancy or when breastfeeding. As a precaution, women who are pregnant or breastfeeding are not permitted to enter the trial and women of childbearing potential will have regular pregnancy tests before, during and after treatment. Patients must agree to adhere with contraceptive requirements laid out in the protocol and Patient Information Sheet. Pregnancies will be reported to UCL CTC, and, if the mother consents, followed up until the outcome is known.

All patients will receive active treatment for their Hodgkin lymphoma. Patients who are not eligible for trial treatment will have standard treatment of their clinician's choice.

All patients will be provided with a patient card which they will be asked to carry with them at all times. This will inform any doctors treating them outside of the trial that they are participating on a clinical trial involving nivolumab and provides contact numbers in case of any medical problems.

Patients will need to attend clinic for treatment every 2 weeks for up to 8 cycles. The follow up schedule does not differ significanctly from the standard follow up schedule for patients who have received salvage treatment for lymphoma. Patients will have up to 3 PET-CT scans during the course of the trial, 2 of which are in excess of standard care. An expert has assessed the radiation risk associated with the scans, and this will be explained to patients in the patient information sheet. Efforts will be made to accredit local PET scanning facilities to minimise the need for patients to travel long distances to have their trial scans.

Patients who are PET positive at the end of nivolumab treatment will be asked to have a repeat biopsy in a site where there is still active disease. This is an invasive surgical procedure in excess of standard care. Patients will be asked to consent for this as an optional element of the study, and may enter the study even if they decline to have a repeat biopsy.

Blood tests for analysis by central laboratories will be taken at the same time as standard blood tests in order to minimise the number of venepunctures the patients need to undergo.

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

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

All patients will receive active treatment for their lymphoma.

If treatment is successful and patients achieve complete metabolic remission, they may benefit from a more successful transplant after nivolumab treatment.

We also hope to learn more about the management of patients with relapsed/refractory Hodgkin lymphoma to inform treatment of patients in future, and to test novel ways of assessing disease response based on blood tests.

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.*

Trial treatment is of a limited duration (up to 8 cycles) and BMS have committed to supply nivolumab for the duration of the trial. Therefore ANIMATE patients will not require treatment with the study drug beyond the end of the research.

Patients will receive the local standard of care for their disease as required after the trial ends.

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

None over and above that of normal practice.

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).*

Members of the direct care team at the participating sites will identify potentially eligible patients via their standard practice, who will then be approached about the trial. Potential patients may also be identified via regional multidisciplinary team meetings, which are held as part of standard NHS practice, and referred to participating sites.

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:
Members of the direct healthcare team at the participating sites may review patient notes as part of the screening process. These staff members are directly involved in patients' medical care and will therefore know the identity of potential trial patients.

UCL CTC will be provided with the patient's initials, date of birth and NHS/CHI number at trial registration. Images sent to the UK PET Imaging Core lab for central review will include the patient's initials, but all other identifiers will be obscured. Samples sent to the central laboratories will be marked with the patient's initials and date of birth. These details will not be shared until the patient has given consent for this information to be sent.

A27-3. Describe what measures will be taken to ensure there is no breach of any duty of confidentiality owed to patients, service users or any other person in the process of identifying potential participants.*Indicate what steps have been or will be taken to inform patients and service users of the potential use of their records for this purpose. Describe the arrangements to ensure that the wishes of patients and service users regarding access to their records are respected. Please consult the guidance notes on this topic.*

Members of the research team at the participating sites, trial staff at UCL CTC, and staff at the UK PET core lab and central laboratories are required to have regular information governance training and good clinical practice refresher courses. All staff are fully aware of the importance of confidentiality to patients.

Sites may contact UCL CTC if they have queries about a potential patient's eligibility, but must not include any patient identifiable information in the correspondence.

UCL CTC staff are trained to immediately dispose of any identifiable personal information received in error from participating sites, and remind research staff that breaches in confidentiality are not acceptable. This correspondence will be kept on file and all patient identifiable personal information for which consent has not been given will be shredded as per the UCL CTC confidentiality SOP.

A27-4. Will researchers or individuals other than the direct care team have access to identifiable personal information of any potential participants?

◉ Yes ○ No

A27-5. Has prior consent been obtained or will it be obtained for access to identifiable personal information?

◉ Yes ○ No

If Yes, please give details below.

Patients' hospital notes may be accessed by representatives of the sponsor for the purpose of trial monitoring. This will be clearly explained in the Patient Information Sheet and patients will explicitly consent to representatives of the Sponsor, including staff at UCL CTC, having access to their notes for this purpose.

UCL CTC will be sent patient initials, NHS/CHI number, sex and date of birth at study registration. Patients will be informed of this in the Patient Information Sheet, and will explicitly consent to this information being shared with the UCL CTC.

The central laboratories (HMDS and UCL Cancer Institute) will be sent the patient's initials, date of birth and trial number when samples are sent. Patients will be informed of this in the patient information sheet and will explicitly consent to this information being shared with the laboratories.

Within each participating NHS site, the study imaging data will remain within the site and stored on NHS computers in keeping with the site's information governance policies. The electronic transfer of scan images and reports from the multiple centres to the sponsor will be coordinated and collated by the UK PET Core Lab. These will be pseudo-anonymised prior to transfer using patient initials and trial number. Patients will be informed of this and will explicitly consent to this information being shared with the UK PET Core Lab. Data transfer methods will use secure transfer protocols with password protection features and encryption. The pseudo-anonymized data collected will be maintained on university computers and in a secure webhosted environment with password protection features and encryption.

The information collected about the patient as part of the trial may be looked at by the regulatory authorities and the NHS Trust/Health Board where the patient is being treated for the purposes of inspection and audit. Patients will be informed of this in the Patient Information Sheet and will explicitly consent for this.

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?

Potential patients will be approached by the local Principal Investigator, or a delegated member of their research team e.g. co-investigator or research nurse. This will be done at a routine clinic visit. The details of the trial will be discussed with the patient, including what will be required of them. Patients will be encouraged to ask questions, and will be given adequate time to do so. It will be made clear that the patient's decision will not affect their future care and that by being approached they are in no way obliged to participate. They will be given the Patient Information Sheet to read and take home to discuss with whom they wish. They will then have another opportunity to ask any questions they may have before signed the consent form.

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.

All patients will have the trial comprehensively explained to them when they are first approached. All details will be discussed, including treatments, risks, benefits, and also the alternatives to taking part in the trial. The patient's clinical care team will ensure that they emphasise that the trial is voluntary and their decision to take part of not will not diminish the level of care that the patient will receive.

Written information will be provided in the form of a Patient Information Sheet which should be given to the patient at least 24 hours prior to consenting wherever possible. The patient information will include contact details, allowing the patient to ask further questions of by their clinical care team. Patients will be encouraged to ask questions or raise any concerns they may have, and to discuss their decision with their family and friends, and, where appropriate, their General Practitioner. The delegated research staff will be available to answer any questions the patient may have.

Patients who decide to enter the trial will then be asked to return to clinic and complete the consent form. Written informed consent will be obtained from the patient by the principal investigator or a delegated member of the research team before any trial specific procedures are undertaken or the patient is registered to the trial. The consent process will be documented in the patient hospital notes. All patients will be given a copy of their consent form to take home and keep for their own reference.

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

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?

Wherever possible, a minimum of twenty four (24) hours will be allowed for the patient to consider and discuss participation in the trial. However, in order to prevent unnecessary return visits, patients may consent to be registered on the same day as being given the information sheet, provided the member of staff taking consent is satisfied that the patient understands the trial and its implications, a member of the research team must then contact the patient in the following days to confirm that they are still willing to participate in the trial, and that confirmation of ongoing consent is documented prior to receiving study drug.

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

If Yes, please give details and justify their inclusion. If Not Known, what steps will you take to find out?

Because patients are undergoing salvage treatment for lymphoma when they are approached for trial, it is possible that they will have received part of their initial or salvage chemotherapy on a clinical trial.

Patients who have previously participated in research, and have either completed the trial or are follow up only will be permitted to take part in the ANIMATE trial. However, patients will not be eligible for Nivolumab treatment on the ANIMATE trial if they have received an experimental treatment within 28 days prior to their planned Nivolumab start date.

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)*

All efforts will be made to enter all eligible patients into the trial. If local interpreters are not available at the site and fully informed consent is not deemed possible, the patient would not be considered for the trial.

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?

If a patient specifically requests patient information in Welsh, sites will be free to use interpreters/advocates and to provide official translations of written patient information in Welsh, where these are available through the NISCHR Permissions Coordinating Unit.

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?

If any such information becomes available during the course of the trial, the UCL CTC will inform all participating research sites and their Principal Investigators.

The clinical care teams at each site will then discuss the relevance of any new data with their individual patients, in order to decide whether or not this affects their continued participation in the trial.

Patients may be asked to reaffirm their consent for the trial if significant new information becomes available during their participation the trial. This is particularly the case if new safety data comes to light that may directly affect the patient.

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
- [ ] Export of personal data outside the EEA
- [ ] 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
- [x] Storage of personal data on any of the following:
  - [x] Manual files (includes paper or film)
  - [x] NHS computers
  - [ ] Social Care Service computers
  - [ ] Home or other personal computers
  - [x] University computers
  - [ ] Private company computers
  - [ ] Laptop computers

Further details:
Access to medical records by those outside the direct healthcare team will be limited to authorised representatives of the Sponsor, regulatory authorities and NHS Trust; this is explained in the Patient Information Sheet, and written informed consent will be obtained for this.

All storage of data on university and NHS computers will be in strict adherence with the Data Protection Act 1998 and Caldicott guidelines.

UCL CTC will be provided with patients' initials, date of birth, sex and NHS/CHI number at registration, to allow for tracking via national health registries if needed. This is explained in the Patient Information Sheet, and written informed consent will be obtained for this.

Paper medical records may be held at site. These form part of the source data for the trial, and as such must remain available during and after the trial. Paper Case Report Forms will be submitted to UCL CTC for trial patients. The data on the forms will be entered onto a database at UCL CTC, and the paper forms will be securely filed – see section A37 for more information.

PET-CT scans will be transferred for central review via a secure server. Patient identifiers will be removed from scans prior to transfer - patients will be identified by initials and trial number only. The images will be filed securely at St Thomas' Hospital, London.

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

Participating trial sites will have their own precautions and protocols that adhere to NHS regulations for the physical storage of data.

All personal data received at UCL CTC is securely locked in filing cabinets when not in use and is only accessible to a

limited number of relevant trained trials staff. Access to the unit is secured with keycards only issued to research staff who work at UCL CTC, and is therefore not open to external personnel. Access to UCL CTC computers is password protected and all activity is traceable and logged by IT services to ensure no wrongdoing and protect data integrity.

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.*

UCL CTC, the central laboratories, central PET scan reviewers and all participating research sites will act to preserve patient confidentiality and will not disclose or reproduce any information by which patients could be identified. The primary means of identifying patients will will be their unique trial number,

The trial will be registered with the Data Protection Officer at University College London in accordance with the Data Protection Act 1998.

UCL CTC will not collect full names or patients' addresses for this trial. Sites will be required to anonymise any patiet identifiable data, such as copies of patient histopathology reports, etc. before sending to UCL CTC.

Access to the trial database will be restricted to a limited number of staff. Data will be stored in a secure manner.

All members of UCL CTC staff working on this trial have signed a UCL Confidentiality Agreement and are familiar with the 1998 Data Protection Act, the UCL Data Protection policy and the UCL CTC Confidentiality Standard Operating Procedure. Staff are required to undertake training and annual assessment of their knowledge of Information Governance.

The Trial Management Group and Independent Data Monitoring Committee will have access to summaries of the data in the form of trial reports, but will not have access to individual patient data.

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.*

Relevant staff at UCL CTC (including Trials Group Lead, Senior Trial Coordinator, Trial Coordinator, Data Manager and Statistician) will have access to the trial data (electronic and paper). This access is required for conducting the trial to the standards of Good Clinical Practice. Consent will be sought for this access.

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 data generated by the study will be analysed by the UCL CTC nominated trials statistician, Amy Kirkwood.

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

	Title	Forename/Initials	Surname
	Professor	Jonathan	Ledermann
Post	Director of CRUK & UCL Cancer Trials Centre		
Qualifications			
Work Address	CRUK & UCL Cancer Trials Centre		
	90 Tottenham Court Road		
	London		
Post Code	W1T 4TJ		
Work Email	j.ledermann@ucl.ac.uk		
Work Telephone	020 7679 9898		
Fax	02076799899		

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:
Study data must be archived for a minimum of 25 years, in accordance with EU Clinical Trials Regulations.

The Sponsor will notify sites when trial documentation held at sites may be archived. All archived documents must continue to be available for inspection by appropriate authorities upon request.

Access will be granted to the research staff directly involved with the trial as well as regulatory authorities or auditors that require access. Data will be stored and destroyed in accordance with ICH GCP guidelines. Both local and central copies will be archived.

It is the Principal Investigator's responsibility to archive their copy on site for the allotted time. Only the Chief Investigator, relevant trial staff and Regulatory Authorities will have access to the centrally stored data once archived.

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

Years: 25
Months: 0

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.*

Research data collected by UCL CTC will be archived at the UCL primary library store in Wickford, Essex. This will remain accessible to the Chief Investigator, relevant trial staff and Regulatory Authorities and can recalled for review.

It is the Principal Investigator's responsibility to archive research data at participating sites in line with local trust policy. Data can be archived off-site but must be accessible to the Chief Investigator, relevant trial staff and Regulatory Authorities upon request.

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 trial is registered with Clinicaltrials.gov which may be used to access information about the study (www.clinicaltrials.gov.com) - reference NCT03337919

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:*

- [x] Peer reviewed scientific journals
- [ ] Internal report
- [x] 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
- [x] Other (please specify)

A lay summary of results will be made available to patients via c linicians and the Cancer Research UK website.

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

UCL CTC will receive patients' initials, date of birth, sex, and NHS/CHI number from participating sites. The trial statistician will not use this data during the analysis, except for identifying patients where further clarification may be required from site staff concerning an anomaly in the data set. The age of participants may be presented in the

published results, but this will only ever be done as stratified data to show the range. Dates of birth will never be explicitly published, nor will the initials of participants. UCL CTC statisticians are trained to not include identifiable personal data when presenting data to the Chief Investigator and the Trial Management Group, who will write the final paper for publication, thus ensuring that this data will not be published.

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.
A lay summary of the results will be prepared by Cancer Research UK in collaboration with the Clinical Trial Coordinator at the UCL CTC and published on the CR UK website.

The summary will be sent out to all research sites. The research team should ensure that they verbally explain the results of the trial to each of their patients if they are still alive and/or their families, and answer any questions raised.

There will also be a formal publication of the results in a peer reviewed journal, which will be available in the public domain.

5. Scientific and Statistical Review

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

- [x] Independent external review
- [x] Review within a company
- [x] Review within a multi−centre research group
- [x] 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 study has also reviewed by the NCRI Lymphoma Clinical Studies Group who have given support to the study.

Bristol-Myers Squibb Pharmaceuticals Ltd, who are providing free nivolumab and funding for the trial have reviewed and approved the study proposal, trial protocol and patient information sheet.

The trial has been designed and developed by the ANIMATE Trial Management Group which includes members who specialise in treating Hodgkin Lymphoma and clinical trials. This group also includes a patient representative, who has been involved in the drafting of the Patient Information Sheet, and advised on aspects of the protocol.

UCL CTC will be coordinating the trial, and has been involved throughout the protocol design and trial setup. The trial has been internally reviewed and approved by UCL CTC's Trial Review Group, which is comprised of senior trials staff, regulatory staff, clinicians and statisticians.

The trial has also been peer reviewed by independent clinicians and statisticians.

The trial protocol has been reviewed by the NCRN Chemotherapy and Pharmacy Advisory Service (CPAS), and the reviewer's suggested changes have been incorporated into the protocol.

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
- [x] Review by a statistician within the research team or multi−centre group
- [ ] Review by educational supervisor
- [ ] 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
	Ms	Amy	Kirkwood
Department	Statistics Group		
Institution	CRUK & UCL Cancer Trials Centre		
Work Address	90 Tottenham Court Road London		
Post Code	W1T 4TJ		
Telephone	02076799231		
Fax	02076799861		
Mobile			
E-mail	a.kirkwood@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?

Overall response rate (ORR) by PET-CT scan following 4-8 cycles of nivolumab

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

• Progression-free survival (PFS) at 1 year
• Overall survival (OS) at 1 year
• Proportion of patients proceeding to stem cell transplantation (autologous or allogeneic)
• Safety & toxicity of nivolumab, particularly autoimmune toxicity, as assessed by CTCAE v.4.0
• OS and PFS stratified by partial metabolic response (PMR) versus complete metabolic response (CMR) on FDG-PET
• Transplant-related mortality and rate of serious complications of allogeneic transplant (grade 3-4 graft-vs-host disease, hyperacute graft-vs-host disease and steroid-responsive febrile syndrome)

Exploratory biological endpoints:
• Correlate PET positive disease with histological evidence of disease on biopsy to establish biopsy negative PMR rate (subject to patient consent)
• Correlate disease response, as assessed by FDG PET and histology, with serological markers, including serum TARC (thymus and activation related chemokine)
• Evaluate the correlation between response to nivolumab and biological parameters e.g. PDL1 expression on Reed-Sternberg cells

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:	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.

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.*

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.

A61. Will participants be allocated to groups at random?

○ Yes ◉ No

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.

ANALYSIS OF THE PRIMARY ENDPOINT
The primary endpoint is the ORR i.e. the proportion of nivolumab treated patients achieving a response (PMR and CMR compared to end of initial salvage scan) after either 4 or 8 cycles. This will be presented as a proportion with 80% confidence intervals.

Any patient without a response scan will be counted as a non-response for the primary analysis (i.e. the denominator will be all eligible nivolumab treated patients). However, a secondary analysis may also be conducted excluding any patient who drops out before the first response scan for reasons other than disease progression or death from disease.

Analysis of the primary endpoint will take place after all patients have finished nivolumab treatment and response data is available.

ANALYSIS OF SECONDARY ENDPOINTS
Survival endpoints:
Progression free survival (PFS):
PFS time will be measured from the date of the PET scan after initial salvage treatment until the date of progression or death (whichever comes first). Patients who are alive and progression free will be censored at the date last seen.

Overall survival (OS):
OS time will be measured from the date of the PET scan after initial salvage treatment until the date of death. Patients who are alive will be censored at the date last seen.

Analysis of PFS and OS will take place once we have 1 year follow-up for all patients. Kaplan Meier survival analyses will be used for both.

Subgroup analyses will be performed for responders and non-responders i.e. do patients with a PMR do worse than those with a CMR after nivolumab treatment. Kaplan Meier survival analysis and Cox regression may be used, although this will be dependent on the numbers of patients with a response and the numbers of events.

PFS and OS will also be analysed by further treatment i.e. did the patient go on to have an allograft or autograft, though we acknowledge that numbers will be very small so analyses will be descriptive.

Complete Metabolic Response (CMR)/Partial Metabolic Response (PMR) rates:
Proportions of patients achieving CMR and PMR will also be presented.

Adverse events:
Analysis will focus on grade 3/4 adverse events. The worst grade seen per patient will be shown for each event type.

Adverse events of special interest will be reported in more detail, with autoimmune events of any grade presented. All analysis will be descriptive.

Transplant related mortality and the rate of serious complications of allo-SCT will presented, though again, it is likely only descriptive statistics will be used.

Other analyses:
The association between pre-nivolumab biological parameters and response to nivolumab will be investigated. As numbers will be very small mostly descriptive statistics will be used i.e. numbers and percentages will be presented for binary/categorical data and means and medians (with ranges) for continuous measurements.

We will also look at changes in TARC levels in responders and non-responders.

PET NEGATIVE PATIENTS NOT TREATED WITH NIVOLUMAB:
We will look at PFS, OS and subsequent treatments for patients who are PET negative post initial salvage treatment.

We will also look at whether there are baseline characteristics at diagnosis or relapse which are associated with response to initial salvage treatment. These will include extranodal disease (at relapse), haemoglobin levels (at relapse), time since the end of first line treatment (to relapse), initial treatment, location of relapse (within RT field or not) and stage (at diagnosis and relapse).

INTERIM ANALYSES:
There are no formal interim analyses or formal stopping rules, but an Independent Data Monitoring Committee (IDMC) will review all trial data yearly and can suggest stopping the trial if they have any concerns about safety or efficacy. Trial Management Group (TMG) meetings will be held approximately every 3-6 months and the committee will review safety data including full SAE listings.

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
	Professor	Peter	Johnson
Post	Professor of Medical Oncology		
Qualifications			
Employer	University Hospital Southampton NHS Foundation Trust		
Work Address	Department of Haematology, Southampton General Hospital		
	Tremona Road		
	Southampton, Hampshire		
Post Code	SO16 6YD		
Telephone			
Fax			
Mobile			
Work Email	johnsonp@soton.ac.uk		

	Title	Forename/Initials	Surname
	Dr	Eve	Gallop-Evans
Post	Consultant Clinical Oncologist		
Qualifications	BSc(Hons), MB.BS, MRCP, PhD, FRCR		
Employer	Velindre NHS Trust		
Work Address	Velindre Cancer Centre		
	Whitchurch		
	Cardiff		
Post Code	CF14 2TL		
Telephone	02920 316246		
Fax			
Mobile			
Work Email	eve.gallop-evans@wales.nhs.uk		

	Title	Forename/Initials	Surname
	Professor	Cathy	Burton
Post	Consultant Haematologist		
Qualifications			
Employer	The Leeds Teaching Hospitals NHS Trust		
Work Address	St James's University Hospital		
	Beckett Street		
	Leeds		
Post Code	LS9 7TF		
Telephone	01132068577		
Fax	01132067468		
Mobile			
Work Email	cathy.burton1@nhs.net		

	Title	Forename/Initials	Surname
	Professor	Karl	Peggs
Post	Professor of Haematology		
Qualifications			
Employer	University College London		
Work Address	UCL Cancer Institute		
	Paul O'Gorman Building, 72 Huntley Street		
	London		
Post Code	WC1E 6JD		
Telephone	02076796500		
Fax			
Mobile			
Work Email	karl.peggs@ucl.ac.uk		

	Title	Forename/Initials	Surname
	Professor	Sally	Barrington
Post	Professor of PET Imaging		
Qualifications			
Employer	Kings College London		
Work Address	School of Biomedical Engineering and Imaging Sciences		
	4th floor Lambeth Wing, St Thomas Hospital, Westminster Bridge Road		
	London		

Post Code	SE1 7EH
Telephone	02071884988
Fax	
Mobile	
Work Email	sally.barrington@kcl.ac.uk

Title	Forename/Initials	Surname
Dr	Laura	Clifton-Hadley

Post	Trial Group Lead
Qualifications	
Employer	University College London
Work Address	CR UK & UCL Cancer Trials Centre 90 Tottenham Court Road London
Post Code	W1T 4TJ
Telephone	02076799860
Fax	02076799861
Mobile	
Work Email	l.clifton-hadley@ucl.ac.uk

Title	Forename/Initials	Surname
Ms	Amy	Kirkwood

Post	Trial Statistician
Qualifications	
Employer	University College London
Work Address	CR UK & UCL Cancer Trials Centre 90 Tottenham Court Road London
Post Code	W1T 4TJ
Telephone	02076799231
Fax	02076799861
Mobile	
Work Email	a.kirkwood@ucl.ac.uk

Title	Forename/Initials	Surname
Dr	Pip	Patrick

Post	Senior Trial Coordinator
Qualifications	
Employer	University College London
Work Address	CR UK & UCL Cancer Trials Centre 90 Tottenham Court Road London
Post Code	W1T 4TJ
Telephone	02076799860
Fax	02076799861
Mobile	
Work Email	p.patrick@ucl.ac.uk

	Title	Forename/Initials	Surname
	Mr	Oliver	Schofield
Post Qualifications	Trial Coordinator		
Employer	University College London		
Work Address	CR UK & UCL Cancer Trials Centre 90 Tottenham Court Road London		
Post Code	W1T 4TJ		
Telephone	02076799860		
Fax	02076799861		
Mobile			
Work Email	o.schofield@ucl.ac.uk		

	Title	Forename/Initials	Surname
	Miss	Lucy	Pike
Post Qualifications	Clinical Scientist (PET - Medical Physicist)		
Employer	Kings College London		
Work Address	School of Biomedical Engineering and Imaging Sciences 4th floor Lambeth Wing, St Thomas Hospital, Westminster Bridge Road London		
Post Code	SE1 7EH		
Telephone	020 7848 7445		
Fax			
Mobile			
Work Email	lucy.pike@kcl.ac.uk		

	Title	Forename/Initials	Surname
	Professor	Arzhang	Ardavan
Post Qualifications	Patient Representative		
Employer	University of Oxford		
Work Address	Clarendon Laboratory Parks Road Oxford		
Post Code	OX1 3PU		
Telephone	01865 272366		
Fax			
Mobile			
Work Email	arzhang.ardavan@physics.ox.ac.uk		

	Title	Forename/Initials	Surname
	Dr	Victoria	Warbey
Post Qualifications	Consultant Radiologist and Nuclear Medicine Physician		
Employer	Kings College London		
Work Address	School of Biomedical Engineering and Imaging Sciences 4th floor Lambeth Wing, St Thomas Hospital, Westminster Bridge Road London		

Post Code	
Telephone	
Fax	
Mobile	
Work Email	Victoria.Warbey@gstt.nhs.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	Nick
Family name	McNally
Address	Joint Research Office, UCL, Gower Street
Town/city	London
Post code	WC1E 6BT
Country	UNITED KINGDOM
Telephone	020 7380 9995
Fax	020 7380 9937
E-mail	ctc.sponsor@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	Bristol-Myers Squibb Pharmaceuticals Ltd.
Address	Unit 2, Sanderson Road Uxbridge Middlesex
Post Code	UB8 1DH
Telephone	01895 523000
Fax	01895 523010
Mobile	
Email	

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

Amount: £1,083,892.00

Duration
Years: 7
Months: 0

If applicable, please specify the programme/ funding stream:

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

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

Name: Cancer Research UK & UCL Cancer Trials Centre

Type of organisation:
( ) NHS (●) Academic ( ) Commercial ( ) Other

Please give further details of sub-contractor and main areas of delegated responsibility: Trial management on behalf of the Sponsor

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
		Heather	House
Organisation	Oxford University Hospitals NHS Foundation Trust		
Address	R&D Department, Oxford University Hospitals NHS Foundation Trust		
	Block 60, Churchill Hospital		
	Oxford		
Post Code	OX3 7LE		
Work Email	ouhtma@ouh.nhs.uk		
Telephone	01865572245		
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:

Thames Valley and South Midlands

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: 01/05/2018
Planned end date: 01/11/2024
Total duration:

Years: 6 Months: 6 Days: 1

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

Planned start date: 01/05/2018
Planned end date: 01/11/2024
Total duration:
Years: 6 Months: 6 Days: 1

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)

End of trial will be declared when the last patient treated with nivolumab has completed three years of follow up.

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 30

Does this trial involve countries outside the EU?

○ Yes ◉ No

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	27
☑ NHS organisations in Wales	1
☑ NHS organisations in Scotland	2
☐ HSC organisations in Northern Ireland	
☐ 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: 30

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?

UCL CTC has undertaken a full risk assessment for the trial, and devised a monitoring plan deemed appropriate for the level of risk involved.

UCL CTC will perform regular central monitoring as outlined in the monitoring plan. Eligibility and compliance with consent requirements will be reviewed in real time via the registration case report form. Other documents will be requested periodically (either as part of regular monitoring requests or on an ad hoc basis), including site delegation logs, accountability logs, sample tracking logs and screening logs. Sites will be asked to perform quality control checks of documentation held in their Investigator Site File and Pharmacy File. Checklists will be provided to facilitate this process. These checks will be supplemented by real-time collection of document receipts when amendments and other important documents are released to sites.

All data received will be reviewed by the trial coordinator and/or data manager and any irregularities will be queried in accordance with the trial data management plan.

All trial data received on CRFs during the course of the trial will also be regularly be reviewed for data quality and any anomalies will be rectified. UCL CTC has additional processes to escalate non-compliance.

'For cause' on-site monitoring will be carried out if there is evidence or suspicion of non-compliance at a site within important aspects of the trial protocol/GCP requirements.

QC checks and internal audits are routinely carried out at UCL CTC to ensure its trials are conducted to appropriate standards. The Sponsor also has a programme of audits, which may include reviews of this trial.

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?

UCL CTC's haematology Independent Data Monitoring Committee will review the study data at least once a year. This will include a review of safety and efficacy data.

Safety data will also be reviewed regularly by the Trial Management Group, who will typically meet every 3-6 months throughout the trial.

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?

The trial may be stopped upon recommendation of the IDMC if they have sufficient concerns about patient safety or the efficacy of the study treatment. Their recommendations will be ratified by an independent Trial Steering Committee.

Sites will be informed in writing by UCL CTC of the reasons for any early closure and the actions to be taken with regards to the treatment and follow up of patients.

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)

The management of the research will be covered by UCL's insurance for negligent harm.

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)

UCL provides cover for negligent harm arising from the design of the research.

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 no legal liability arises.

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 Opdivo

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

Trade name:
Opdivo
EV Product Code
Name of the MA holder:
Bristol-Myers Squibb Pharma EEIG
MA number (if MA granted by a Member State):
EU/1/15/1014/001-002
Is the IMP modified in relation to its MA?
○ Yes ◉ No ○ Not Answered

Which country granted the MA?
EUROPEAN UNION
Is this the Member State concerned with this application?
◉ 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

Specify which Member States:

AUSTRIA	☐	BELGIUM	☐	BULGARIA	☐	CYPRUS	☐
CZECH REPUBLIC	☐	DENMARK	☐	ESTONIA	☐	FINLAND	☐
FRANCE	☐	GERMANY	☐	GREECE	☐	HUNGARY	☐
ICELAND	☐	IRELAND	☐	ITALY	☐	LATVIA	☐
LIECHTENSTEIN	☐	LITHUANIA	☐	LUXEMBOURG	☐	MALTA	☐
NETHERLANDS	☐	NORWAY	☐	POLAND	☐	PORTUGAL	☐
ROMANIA	☐	SLOVAKIA	☐	SLOVENIA	☐	SPAIN	☐
SWEDEN	☐	UNITED KINGDOM	☑				

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	Opdivo
Product code where applicable	BMS-936558
ATC codes, if officially registered	L01XC17
Pharmaceutical form (use standard terms)	Concentrate 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	Nivolumab is given on day 1 of each 14 day cycle. Patients will undergo up to 8 cycles of treatment (total duration of treatment approximately 4 months)

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	240mg
Specify per day or total	◉ per day ◯ total ◯ Not Answered
Specify total dose (number and unit)	1920 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):	Nivolumab
CAS number:	946414-94-4
Current sponsor code:	
Other descriptive name:	
Full Molecular formula	C6362H9862N1712O1995S42
Chemical/biological description of the Active Substance	Nivolumab is a monoclonal antibody, a type of protein designed to recognise and attach to a specific target substance in the body. Nivolumab attaches to a target protein called programmed death-1 receptor (PD-1) that can switch off the activity of T cells (a type of white blood cell that forms part of the immune system, the body's natural defences). By attaching to PD-1, nivolumab blocks its action and prevents it from switching off your T cells. This helps increase their activity against the cancerous cells.

Strength

Concentration unit:	mg/l milligram(s)/litre
Concentration type:	equal
Concentration number (only use both fields for range):	10 mg/mL

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. Nivolumab is a human monoclonal antibody that targets the programmed death-1 (PD-1) CD279 cell surface membrane receptor. PD-1 is a negative regulatory molecule expressed by activated T and B lymphocytes.1 Binding of PD-1 to its ligands, PDL1)
and PD-L2, results in the down-regulation of lymphocyte activation. Inhibition of the interaction between PD-1 and its ligands promotes immune responses and antigenspecific
T-cell responses to both foreign antigens as well as self-antigens.

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

Importer

Organisation	Bristol-Myers Squibb Pharmaceuticals Ltd
Address	BMS House, Uxbridge Business Park, Sanderson Road
Town/city	Uxbridge
Post code	UB8 1DH
Country	UNITED KINGDOM

Give the manufacturing authorisation number

If no authorisation, give the reasons:
Information pending

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

IMP
PR1

RS2

Manufacturer

Organisation	Bristol-Myers Squibb S.r.l.
Address	Loc. Fontana del Ceraso
Town/city	Anagni (FR)

Post code 03012

Country ITALY

Give the manufacturing authorisation number

If no authorisation, give the reasons:
Information pending

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

IMP
PR1

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

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. The ARSAC research application form can be launched from the Site-Specific Information Form for the site in IRAS.

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)*
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

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

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

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 Ms Lucy Pike on 11/01/2018 12:00.

Job Title/Post:	Clinical Scientist
Organisation:	King's College London
Email:	lucy.pike@kcl.ac.uk

C3. Details of person acting as lead Medical Physics Expert

Title	Forename/Initials	Surname
Ms	Lucy	Pike

Post	Clinical Scientist
Details of clinical scientist registration with the Health Professions Council:	
Registration no	CS17241
Organisation	Kings College London
Address	Kings College London and Guy's and St Thomas' PET Centre
	School of Biomedical Engineering and Imaging Sciences 4th floor Lambeth Wing St Thomas Hospital
	Westminster Bridge Road, London
Post Code	SE1 7EH
Telephone	020 7188 4988
Fax	020 7620 0790
Mobile	
Email	lucy.pike@kcl.ac.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.

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

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 Sally Barrington on 11/01/2018 12:04.

Job Title/Post:	Professor of PET Imaging
Organisation:	Kings College London
Email:	sally.barrington@kcl.ac.uk

D4. Details of lead Clinical Radiation Expert

	Title	Forename/Initials	Surname
	Professor	Sally	Barrington
Post	Professor of PET Imaging		
Details of professional registration	(●) General Medical Council ( ) General Dental Council		
Registration no	3258600		
Organisation	Kings College London		
Address	Kings College London and Guy's and St Thomas' PET Centre School of Biomedical Engineering and Imaging Sciences 4th floor Lambeth Wing St Thomas Hospital Westminster Bridge Road, London		
Post Code	SE1 7EH		
Telephone	020 7188 4988		
Fax	020 7620 0790		
Mobile			
Email	sally.barrington@kcl.ac.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?

Formalin fixed paraffin embedded tumour blocks from a previous biopsy (either at relapse or initial diagnosis; stored in site pathology archives).

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.

The tissue block from the patient's previous tumour biopsy (either a biopsy performed at time of relapse or the biopsy from their initial diagnosis) will have been collected before the patient would have been made aware of the ANIMATE trial. The consent signed by the patient when they underwent their biopsy may have contained a caveat covering the use of the sample for future research, but this will likely vary between participating sites, based on local policy. Therefore, UCL CTC cannot confirm whether consent has been given for all samples, although it is likely that it will have been given for some. Regardless of whether consent has been given for use in research previously, permission to use these samples for analysis in the study will be sought as part of the consent process for the trial.

Samples will not be sent to the central laboratory until patients have consented for, and been registered into, the trial.

5. Is it proposed to seek further consent to use the samples in this research?

◉ Yes ○ No

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?

3µm sections of the tissue block will be taken and immunohistochemistry performed. A panel of markers will be assessed for each case including: CD30, IRF-4, PAX-5, CD20, CD3, OCT-2, BCL-6, CD79, CD15, and LMP-1. Immunostaining for PD1, PD-L1 and PD-L2 will be performed in most cases.

Sections of the block will also be prepared for fluorescent in-situ hybridisation (FISH) studies. The FISH studies conducted will include those for 9p24 abnormalities as these have previously been reported to be highly predictive of outcome. Probes will include CD274/PD-L1, PDCD1LG2/PD-L2, CEP9 and REL. Fifty Reed-Sternberg cells per slide will be reviewed and the FISH signals defined as disomic, polysomic, relative copy gain or amplified.

Gene expression profiling (GEP) will be performed using either or both of the HTG Immunopanel and the Affymetrix Human Transcriptome Array, which is a whole transcriptome array. These are two gene expression platforms currently being used in HMDS with bioinformatic support from within HMDS and in collaboration with the University of Leeds.

FFPE tissue will also be sent from HMDS, Leeds to the UCL Cancer Institute, where further exploratory immunohistochemical analysis will take place.

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

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

Tissue blocks will be held at the Haematological Malignancy Diagnostic Service (HMDS) in Leeds, who will analyse the samples.

Designated laboratory staff at the central laboratory will be responsible for preserving the condition of the samples and for ensuring security and confidentiality of the samples and any linked data. Only the designated staff will have access to the samples.

Following analysis at HMDS, samples will be sent to UCL Cancer Institute for additional immunohistochemistry analysis by designated staff within that laboratory.

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:

FFPE Blocks will be stored at HMDS for use in ethically approved research unless (1) the patient declines to consent for this or (2) the site asks for blocks to be returned.

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?

- Formalin fixed paraffin embedded (FFPE) block from tumour biopsy (if PET positive after 8 cycles and patient has consented).

- FFPE block from tumour biopsy at relapse post nivolumab (if clinically indicated).

- Peripheral blood samples (up to 6 per patient).

2. Who will collect the samples?

Tumour biopsies will be obtained by a surgeon at the local site.

Blood samples will be obtained by a member of medical or nursing staff at the local site.

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

If Yes, say who will have access to the code and personal information about the donor.

Principal Investigator, Co-investigator and research staff at site who are directly involved in processing of samples, and appropriate staff at UCL Cancer Trials Centre.

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?

TUMOUR BIOPSIES (FFPE blocks)
3µm sections of the tissue block will be taken and immunohistochemistry performed. A panel of markers will be assessed for each case including: CD30, IRF-4, PAX-5, CD20, CD3, OCT-2, BCL-6, CD79, CD15, and LMP-1. Immunostaining for PD1, PD-L1 and PD-L2 will be performed in most cases.

Sections of the block will also be prepared for fluorescent in-situ hybridisation (FISH) studies. The FISH studies conducted will include those for 9p24 abnormalities as these have previously been reported to be highly predictive of outcome. Probes will include CD274/PD-L1, PDCD1LG2/PD-L2, CEP9 and REL. Fifty Reed-Sternberg cells per slide will be reviewed and the FISH signals defined as disomic, polysomic, relative copy gain or amplified.

Gene expression profiling (GEP) will be performed using either or both of the HTG Immunopanel and the Affymetrix Human Transcriptome Array, which is a whole transcriptome array. These are two gene expression platforms currently being used in HMDS with bioinformatic support from within HMDS and in collaboration with the University of Leeds.

UCL Cancer Institute will also carry out further exploratory immunohistochemical analysis on the samples.

PERIPHERAL BLOOD SAMPLES
Multicolour flow panels will be performed on the blood to identify immune signatures prior to, during, and after nivolumab treatment.

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.

TUMOUR BIOPSIES (FFPE blocks)
FFPE Tissue blocks will be held at the Haematological Malignancy Diagnostic Service (HMDS) in Leeds, who will analyse the samples.

Designated laboratory staff at the central laboratory will be responsible for preserving the condition of the samples and for ensuring security and confidentiality of the samples and any linked data. Only the designated staff will have access to the samples.

Following analysis at HMDS, blocks will be sent to UCL Cancer Institute for additional immunohistochemistry analysis by designated staff within that laboratory.

PERIPHERAL BLOOD SAMPLES
Peripheral blood samples will be sent to the Immune Regulation and Tumour Immunotherapy laboratory at UCL Cancer Institute, where designated staff will undertake analysis. It is not anticipated that there will be any material left over following 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:

TUMOUR BIOPSIES (FFPE blocks)
FFPE Blocks will be stored at HMDS for under use in ethically approved research unless (1) the patient declines to consent for this or (2) the site asks for blocks to be returned.

PERIPHERAL BLOOD SAMPLES
It is not anticipated that there will be any leftover material once analysis for the trial has been completed.

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 Country: England		Forename Middle name Family name Email Qualification (MD...) Country	Graham Collins Graham.collins@ouh.nhs.uk MBBS, MRCP (UK), FRCPath, DPhil UNITED KINGDOM
	Organisation name	Oxford University Hospitals NHS Foundation Trust		
	Address	Churchill Hospital, Old Way, Headington Oxford HEADINGTON OXFORD OXFORDSHIRE		
	Post Code	OX3 7LE		
IN2	◉ NHS site ○ Non-NHS site Country: England		Forename Middle name Family name Email Qualification (MD...) Country	Kirit Ardeshna kiritardeshna@nhs.net UNITED KINGDOM
	Organisation name	University College London Hospitals NHS Foundation Trust		
	Address	University College Hospital, 235 Euston Road London LONDON GREATER LONDON		
	Post Code	NW1 2BU		
IN3	◉ NHS site ○ Non-NHS site		Forename Middle name Family name	Eve Gallop-Evans

Country: Wales

Email	eve.gallop-evans@wales.nhs.uk
Qualification (MD...)	BSc. MBBS, FRCR (UK), PhD, FRCR (UK)
Country	UNITED KINGDOM

Institution name	Cardiff and Vale UHB - University Hospital of Wales
Department name	Oncology Department
Street address	University Hospital of Wales, Heath Park
Town/city	Cardiff
Post Code	CF14 4XW

IN4

- (●) NHS site
- ( ) Non-NHS site

Country: Scotland

Forename	Pam
Middle name	
Family name	McKay
Email	pam.mckay@ggc.scot.nhs.uk
Qualification (MD...)	MBChB, MRCP (UK), FRCP, MRCPath, FRCPath
Country	UNITED KINGDOM

Institution name	Greater Glasgow & Clyde Health Board - Beatson West of Scotland Cancer Centre
Department name	Department of Haematology
Street address	Beatson West of Scotland Cancer Centre, 1053 Great Western Road
Town/city	Glasgow
Post Code	G12 0YN

IN5

- (●) NHS site
- ( ) Non-NHS site

Country: England

Forename	Kim
Middle name	
Family name	Linton
Email	Kim.linton@manchester.ac.uk
Qualification (MD...)	MBChB, MRCP, PhD
Country	UNITED KINGDOM

Organisation name	The Christie NHS Foundation Trust
Address	Christie Hospital, Wilmslow Road
	Withington, Manchester
	MANCHESTER GREATER MANCHESTER
Post Code	M20 4BX

IN6

- (●) NHS site
- ( ) Non-NHS site

Forename	Wendy
Middle name	

Country: England

Family name	Osborne
Email	Wendy.Osborne@nuth.nhs.uk
Qualification (MD...)	
Country	UNITED KINGDOM

Organisation name	Newcastle upon Tyne Hospitals NHS Foundation Trust
Address	Freeman Hospital, Freeman Road Newcastle upon Tyne HIGH HEATON NEWCASTLE-UPON-TYNE TYNE AND WEAR
Post Code	NE7 7DN

IN7

(●) NHS site
( ) Non-NHS site

Country: England

Forename	Shankara
Middle name	
Family name	Paneesha
Email	shankara.paneesha@nhs.net
Qualification (MD...)	FRCP. FRCPath, MRCP (UK), MD (General Medecine), Diplomate of National Board (India), MBBS
Country	UNITED KINGDOM

Organisation name	Heart of England NHS Foundation Trust
Address	Birmingham Heartlands Hospital, Bordesley Green East Birmingham BIRMINGHAM WEST MIDLANDS
Post Code	B9 5ST

IN8

(●) NHS site
( ) Non-NHS site

Country: England

Forename	Andrea
Middle name	
Family name	Kuhnl
Email	Andrea.Kuhnl@nhs.net
Qualification (MD...)	MD
Country	UNITED KINGDOM

Organisation name	King's College Hospital NHS Foundation Trust
Address	King's College Hospital, Denmark Hill London LONDON GREATER LONDON
Post Code	SE5 9RS

IN9

- (●) NHS site
- ( ) Non-NHS site

Country: England

Organisation name	University Hospitals of Leicester NHS Trust
Address	Leicester Royal Infirmary, Infirmary Square Leicester LEICESTER LEICESTERSHIRE
Post Code	LE1 5WW

Forename	Fiona
Middle name	
Family name	Miall
Email	fiona.miall@uhl-tr.nhs.uk
Qualification (MD...)	BMedSci, BMBS, MRCPath, FCRPath
Country	UNITED KINGDOM

IN10

- (●) NHS site
- ( ) Non-NHS site

Country: England

Organisation name	London North West Healthcare NHS Trust
Address	Northwick Park Hospital, Watford Road Harrow HARROW MIDDLESEX
Post Code	HA1 3UJ

Forename	Charalampia
Middle name	
Family name	Kyriakou
Email	c.kyriakou@nhs.net
Qualification (MD...)	MD, PhD
Country	UNITED KINGDOM

IN11

- (●) NHS site
- ( ) Non-NHS site

Country: England

Organisation name	Norfolk & Norwich University Hospitals NHS Foundation Trust
Address	Colney Lane, Colney Norwich, Norfolk NORWICH NORFOLK
Post Code	NR4 7UY

Forename	Nimish
Middle name	
Family name	Shah
Email	NIMISH.SHAH@nnuh.nhs.uk
Qualification (MD...)	MbbCH BAO, MRCP, FRCPath, MD
Country	UNITED KINGDOM

IN12

◉ NHS site
○ Non-NHS site

Country: England

Organisation name	Royal Cornwall Hospitals NHS Trust
Address	Royal Cornwall Hospital, Treliske Truro TRELISKE TRURO CORNWALL
Post Code	TR1 3LJ

Forename	Bryson
Middle name	
Family name	Pottinger
Email	bryson.pottinger@nhs.net
Qualification (MD...)	MBChB, MRCP, FRCPath
Country	UNITED KINGDOM

IN13

◉ NHS site
○ Non-NHS site

Country: England

Organisation name	SHEFFIELD TEACHING HOSPITALS NHS FOUNDATION TRUST
Address	Royal Hallamshire Hospital, Glossop Road Sheffield SHEFFIELD SOUTH YORKSHIRE
Post Code	S10 2JF

Forename	Nick
Middle name	
Family name	Morley
Email	nick.morley@sth.nhs.uk
Qualification (MD...)	MRCPath, MRCP, MB.BS. BA
Country	UNITED KINGDOM

IN14

◉ NHS site
○ Non-NHS site

Country: England

Organisation name	Bart's Health NHS Trust
Address	St Bartholomew's Hospital, West Smithfield

Forename	Rifca
Middle name	
Family name	Le Dieu
Email	Rifca.LeDieu@bartshealth.nhs.uk
Qualification (MD...)	
Country	UNITED KINGDOM

	London
	LONDON GREATER LONDON
Post Code	EC1A 7BE

IN15

- (●) NHS site
- ( ) Non-NHS site

Country: England

Forename	Ruth
Middle name	Pettengell
Family name	Pettengell
Email	rpetteng@sgul.ac.uk
Qualification (MD...)	
Country	UNITED KINGDOM

Organisation name	St George's University Hospitals NHS Foundation Trust
Address	St George's Hospital, Blackshaw Road
	London
	TOOTING LONDON GREATER LONDON
Post Code	SW17 0QT

IN16

- (●) NHS site
- ( ) Non-NHS site

Country: England

Forename	Cathy
Middle name	
Family name	Burton
Email	cathy.burton1@nhs.net
Qualification (MD...)	BA(Hons), MBBChir, MRCP, FRCPath, MD
Country	UNITED KINGDOM

Organisation name	Leeds Teaching Hospitals NHS Trust
Address	St James' University Hospital, Beckett Street
	Leeds
	LEEDS WEST YORKSHIRE
Post Code	LS9 7TF

IN17

- (●) NHS site
- ( ) Non-NHS site

Country: England

Forename	Deborah
Middle name	
Family name	Turner
Email	deborah.turner2@nhs.net
Qualification (MD...)	BSc, MBBS, MRCP, MRCPath, FRCPath, PCGE

			Country	UNITED KINGDOM
	Organisation name	Torbay and South Devon NHS Foundation Trust		
	Address	Torbay Hospital, Lowes Bridge Torquay, Devon NEWTON ROAD TORQUAY DEVON		
	Post Code	TQ2 7AA		

IN18

(●) NHS site
( ) Non-NHS site

Country: England

Forename	Paul		
Middle name			
Family name	Fields		
Email	paul.fields@gstt.nhs.uk		
Qualification (MD...)			
Country	UNITED KINGDOM		
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		

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 Graham Collins on 11/01/2018 12:37.

Job Title/Post:	consultant
Organisation:	Oxford University Hospitals
Email:	graham.collins@ouh.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 Miss Nicole Gower on 11/01/2018 12:06.

Job Title/Post:	Regulatory Manager - Quality
Organisation:	CR UK and UCL CTC
Email:	r.beehag@ucl.ac.uk