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)
Non invasive optic techniques in neurosurgery

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. 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

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

a) Does the study involve the use of any ionising radiation?	( ) 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

d) Will the study involve any other clinical procedures with participants (e.g. MRI, ultrasound, physical examination)? ○ 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?

- ☑ IRAS Form
- ☐ Confidentiality Advisory Group (CAG)
- ☐ Her Majesty's Prison and Probation Service (HMPPS)

Most research projects require review by a REC within the UK Health Departments' Research Ethics Service. Is your study exempt from REC review?

○ Yes ◉ No

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 Collaboration for Leadership in Health Research and Care (CLAHRC), NIHR Patient Safety Translational Research Centre or Medtech and In Vitro Diagnostic Cooperative 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 Basic science study involving procedures with human participants

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)
Non invasive optic techniques in neurosurgery

PART A: Core study information

1. ADMINISTRATIVE DETAILS

A1. Full title of the research:

Non-invasive optic techniques in neurosurgery - Use of multispectral, hyperspectral imaging, and fluorescence technology during neuro-oncology and neuro-vascular surgery

A3-1. Chief Investigator:

Title Forename/Initials Surname	[TITLE] [FORENAME] [SURNAME]
Post	Consultant Neurosurgeon
Qualifications	BSc MB BS FRCS(SN)
ORCID ID	
Employer	Imperial College NHS Trust
Work Address	Fulham Palace oad Hammersmith
Post Code	W6 8RF
Work E-mail	[EMAIL]
* Personal E-mail	
Work Telephone	[TELEPHONE]
* Personal Telephone/Mobile	
Fax	[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

[TITLE] [FORENAME] [SURNAME]

Address	Norfolk Place Room 221, Medical School Building, St Marys Campus London
Post Code	W2 1PG
E-mail	[EMAIL]
Telephone	[TELEPHONE]
Fax	[FAX]

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:

Protocol Version:

Protocol Date:

Funder's reference number (enter the reference number or state not applicable):

Project website:

Registry reference number(s):

TheUK Policy Framework forHealth and Social Care Research sets out the principle of making information about research publicly available. 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):

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 present study aims to investigate the potential application of multispectral analysis, hyperspectral imaging, and fluorescence during neurosurgical procedures, specifically during brain tumour resection and neurovascular procedures (aneurysm clipping / intra-extracranial bypasses, vascular malformation resection). These optics techniques are entirely non-invasive and consist in a series of cameras an filters to be used together with the standard microsurgical and endoscopic instruments used in theatre. The research procedure consists of images

acquisition and data processing, with virtually no additional invasive procedures to be performed on patients.

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, R&D office 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.

Multispectral and hyperspectral analysis – basic components and mechanism of action

Multispectral and hyperspectral imaging analysis is a technology based on the analysis of light reflected by tissues. It is used to separate specific wavelengths ranges across the electromagnetic spectrum. By doing so, it can identify wavelengths invisible to the naked eye, and make them visible by applying specific filters. The main difference between the multispectral and hyperspectral imaging is the number of wavelengths processed: the first technique selects a relatively small number of broad spectra, while the latter shows a larger number of spectra with smaller extension. Both techniques are based on the same technology.
The system consists of the following basic components:
• a xenon light source
• a camera
• surgical instruments used for magnification during the procedure (either an endoscope or a microscope)
• a series of filters
• a computer
The xenon light source is connected to a surgical magnifying device, as standard practice during every surgical procedure. The light source is indispensable to correctly visualize the surgical field and magnify micro-components (such as small vessels, cavities, and nerves) poorly or not visible to the naked eye. A series of filters are applied in front of the light source. These filters are responsible for separating different wavelengths coming from the surgical field (see below). The whole system is connected to a camera for images acquisition, and this is in turn connected to a computer for elaboration. Images are processed onto three orthogonal planes, thus allowing 3D reconstruction of the analyzed area.

Any visible object, including human body tissues, absorbs light when hit by a light beam. A small portion (wavelength) of the light beam is always reflected back to the observer. This specific wavelength reflected back corresponds to a specific colour, and this is the reason why any object we see shows a unique colour: that object does not absorb that particular wavelength, which our eye perceives as a colour. perfect example of this is blood: its colour is red because it tends to reflect back to us the wavelength of light corresponding to the colour red. However, wavelengths corresponding to colours are actually not set as specific numbers, and they should not be considered as rigid boxes with defined boundaries between a colour and another: there is a continuous spectrum of a huge number of wavelengths, each one fading into another. Coming back to the blood example, oxygenated (arterial) blood looks brighter than the one with no oxygen (deoxygenated blood, or venous blood). However, when analyzing blood during tissues perfusion (that is, blood going into body organs such heart, liver or brain), the proportion of oxygenated and deoxygenated blood varies, and the two tend to be mixed. To the naked eye, this proportion is invisible. Multispectral technology, however, can separate even minimal differences in wavelengths and identify this proportion with great accuracy.

Fluorescence - basic components and mechanism of action

Fluorescence is defined as the emission of light by a substance that has absorbed light or another electromagnetic radiation. It can be distinguished in endogenous and exogenous fluorescence. Endogenous fluorescence of human tissue is too weak to be used in clinical practice. Exogenous fluorescence consists of the administration of ligand-binding compounds targeting specific human molecules and react to defined wavelengths of the electromagnetic spectrum. Once the compound is bound to its target, it emits light that can be detected by the operating microscope. Exogenous fluorescence is routinely used in neuro-oncology and neurovascular surgery, for different purposes. Clinical applications include, specifically:
- 5-ALA (Gliolan) fluorescence consists of oral administration of 5-Amino-Levulinic Acid (5-ALA) to brain tumour patients prior to their surgery - there is evidence that binding of the molecule on tumour tissue can be used as an additional tool to help to guide resection under ultraviolet light - this is now a standard feature in operating microscopes;
- fluorescein and indocyanine green - these compounds are used in vascular and neuro-oncology surgery to study differences in perfusion between tumour and brain tissue, or to check brain perfusion after by-pass or clipping procedures - they are used under infrared light, which is also a standard feature of operating microscopes.

Clinical applications

Multispectral analysis has already been used in lung, colon and head, and neck surgery. The primary use of this technology is the identification of subtle differences in blood perfusion (mostly blood volume), as well as a proportion between oxygenated and deoxygenated blood in tumours as compared to the one in normal tissues. Preliminary results show different blood volumes and oxygenation rates in different tissues, meaning that the technology can be used to study discrepancies in the appearance of tumour tissue as opposed to normal mucosa.
The multispectral analysis could be particularly valuable in the field of neurosurgery, specifically malignant tumours surgery.
The main application we would test this technology on is surgery for malignant tumours located close to eloquent/functional areas of the brain. Previous studies on functional MRI scans showed that, during execution of a task (e.g. moving a limb, speaking, following an object with eyes), specific brain areas activation produces changes in blood volume and ratio between oxygenated / deoxygenated blood. We would aim to use multispectral analysis during awake and asleep surgical procedures for tumour resection. Surgery on awake patients is a standard procedure in neuro-oncology, at it involves waking the patient up during the procedure to test eloquent areas of the brain around a tumour through neurophysiological stimulation. This technique maximizes the amount of tumour that can be resected and at the same time significantly reduces the possibility of injuring functional/eloquent areas of the brain, such as the speech or the motor areas.

Our hypothesis is that multispectral analysis can help to identify functional areas of the brain to guide tumour resection, and can be as reliable as the fMRI scan. If proven so, this would be a benchmark study to:
1) improve the extent of resection of brain tumours, which translate into an improved response to treatment and ultimately an improved prognosis;
2) validate and potentially improve fMRI technology for future studies;
3) improve knowledge and deep understanding of physiological brain activation during simple tasks execution;
4) potentially provide a tool to expand our knowledge on even more complex brain functions, such as cognition, memory, personality, and potentially produce improved functional outcome for our patients even regarding high cognitive functions.
Another potential application of multispectral imaging regards the study of blood vessels architecture in malignant and benign intracranial tumours. We know from the histological and radiological literature that malignant brain tumours tend to have abnormal blood flow due to the pathological formation of blood vessels on the tumour capsule. As previously mentioned, the brain tissue surrounding the tumour is often invaded by tumour cells, and detecting the amount and the extent of brain invasion is challenging for a surgeon. Our hypothesis is that, by analysing invaded brain through multispectral analysis, we would be able to detect changes in blood flow and/or oxygenated /deoxygenated ratio. This would guide the surgical procedure by pushing the boundaries further and allow a more extensive resection to improve patient prognosis and outcome.
Finally, we can potentially apply the same technology to vascular neurosurgery procedures. During vascular surgery, large blood vessels are manipulated, sometimes cut and sutured together. These blood vessels usually supply extended and crucial portions of the brain. Multispectral and hyperspectral analysis can help to assess the degree of brain perfusion following the procedure, thus contributing to intraoperatively revise the procedure to timely avoid any hypoperfusion/ischemia. A classical example of this would be aneurysm clipping. Aneurysms are small, balloon-like dilatation of brain arteries, that can burst and cause significant hemorrhage. They are usually treated through endovascular coiling, that is: positioning of coilings inside the dilatation to cause thrombosis and exclude it from the blood circulation. However, in selected cases this is not possible, therefore a surgical procedure through a craniotomy is performed and the aneurysm is closed with a metal clip. Sometimes clip positioning can be challenging, and the clip itself can trap one or more arterial branches feeding supplied brain. This complication can result in ischemia, which can be more or less severe depending on the caliber and position of the arterial branch. There are several standardized techniques to test perfusion and blood supply. These include the injection of fluorescent dye or intra-operative doppler check on the arteries to assess blood flow. However, multispectral analysis can provide a novel and potentially non-invasive technique to assess tissue perfusion. Same concepts apply for intra-extracranial bypasses for vascular stenosis or giant aneurysms. The current fluorescence techniques could be potentially combined with multispectral/hyperspectral analysis.

We are planning to prospectively enroll cases of patients undergoing tumour surgery and neurovascular procedures and apply multispectral and hyperspectral imaging during the procedure. Selection of patients will be performed following the inclusion criteria (see below). Data obtained will be acquired and processed through dedicated software. We are also planning to combine multispectral analysis and fluorescence techniques on all patients where fluorescence will be used, as per clinical indications.

Potential issues

Multispectral and hyperspectral imaging are two entirely non-invasive techniques. There is no delivery of any electromagnetic radiation implied other than the ones given with standard neurosurgical instruments, such as a

microscope or endoscope. Both of these instruments use visible light to function.
There are three potential problems.
1. The incongruity between spectral and clinical findings / histological analysis. It is possible that multispectral imaging will produce false positives or false negatives, which is: eloquent areas that are not identified as such using standard clinical tools, or abnormal oxygenation/deoxygenation ratios that are not confirmed by intra-operative findings. Therefore, no spectral data will be considered in the clinical decision-making process.
2. Increased length of surgical procedures. Based on existing literature, the acquisition of image data takes about 200 milliseconds per image, meaning 3,2 seconds for a set of 13 images. Even considering the worst case scenario of the acquisition of multiple sets of 20 images, this technology should not add more than 5 minutes per case. In most cases, a negligible increasing time of 1 to 2 mins more per procedure will be required.
3. The economic cost to NHS. As above, the sampling of these patients may extend operating time, thereby impacting on the delivery of service to the NHS. We, therefore, estimate that in a full day operating list consisting of 2 tumour patients, a total of 10 minutes of acquisition/analysis time will be required, with no significant impact on the delivery of NHS care.

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)

Validation study

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

Can multispectral/hyperspectral analysis detect subtle changes in blood supply of brain tumours, eloquent/functional brain areas surrounding the tumours?

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

Can multispectral/hyperspectral analysis detect changes in brain blood supply and oxygenation following neurovascular procedures, such as aneurysm clipping or intra-extracranial bypasses?

Can this technique be improved to become a reliable clinical tool during neurosurgical procedures?

Can this technique be integrated with different spectroscopic or non-spectroscopic techniques to refine the precision of brain tumours resection?

Can the combination of multispectral/hyperspectral analysis and fluorescence provide useful new insight into the detection of different perfusion patterns of brain tumours VS normal brain tissue? Can the same concept apply to neurovascular surgery to detect subtle perfusion changes after aneurysmal clipping / AVM resection/bypass performances?

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

Surgical resection of brain tumours remains a challenge. While the center of a tumour is easily resectable, its margins are often fading into normal brain, and therefore quite difficult to identify. Moreover, there is now extensive literature proving that tumour cells extend way beyond visible margins of a tumour, following white matter tracts in the brain. As opposite to different organs (such as liver or kidney), resection of brain tumours beyond the visible margins is limited by the presence of eloquent/functional areas. Damages or resection of these areas will inevitably cause a permanent disability, which can be incredibly serious and impact on further treatment: a paralyzed or unconscious patient is not capable of tolerating chemotherapy or radiotherapy after surgery, both crucial complementary forms of treatment to contain the disease, in combination with surgery.
Because of these premises, the concept of "functional margins of resection" is now established in the neurosurgical community: a tumour is resected and the resection is pushed up to 1-2 cms beyond the margins or only up to the point where a functional/eloquent area is found. If the latter is the case, the functional area is obviously preserved and tumour resection is stopped. Identifying these areas is the main challenge in brain tumour surgery.
The aim of this study and its scientific justification is to refine a new, potentially more practical and quick technique to identify functional brain areas in real time. This study can serve as a benchmark study to both improve surgery of brain tumours and increase our knowledge about brain tumours and eloquent brain vascular supply. This technique can also potentially be implemented to obtain a novel technology to assess brain perfusion during neurosurgical procedures. Maintaining blood supply to healthy brain tissue is a key component of successful neuro-oncological and neurovascular surgery. Multispectral/hyperspectral analysis can be evaluated as a complementary tool to assess brain perfusion in real-time and prevent post-operative devastating neurological complications, such as strokes, or significantly reduce the secondary damage would these complications occurr.

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

The present project consists of a pilot observational study on patients diagnosed with brain tumours and/or neurovascular disease candidate for a neurosurgical operation.

The present study will include:
• In vivo microscopic and/or endoscopic multispectral/hyperspectral analysis
• In vivo microscopic and/or endoscopic fluorescence (using either infrared light - IR - or ultraviolet light, depending on the clinical indication of the specific case
• In vivo microscopic and/or endoscopic fluorescence combined with multispectral/hyperspectral analysis

During surgery, the operating surgeon will be using standard neurosurgical equipment such as an endoscope and/or a microscope. From the surgeon’s point of view, this equipment is operated in exactly the same way as the standard surgical equipment. The only modification would be that either the microscope or the endoscope in use will be connected to the system of camera and filters for multispectral/hyperspectral analysis.

Use of this imaging acquisition technique will not change standard operative practice, nor will it interfere with the principles of neurological surgery. During each surgical intervention, tissue-specific spectral data will be collected. It is important that there is a method of comparing the spectral data generated by multispectral imaging to the nature of the tissue being dissected. In order to do this, we plan to visually record the operation in order to sync visual data with the spectral data obtained at the same moment in time. The video recording will not be patient identifiable and will be viewed only by members of the research team working on this project. The images will be stored on Imperial College Computers at Charing Cross Hospital and Hammersmith Hospital. The use of video recording equipment will be included in the patient information sheet given to all patients prior to gaining consent.

Intra-operative imaging data and spectra will be collected during tumour resection. Surgery will be conducted following standard procedures, already validated in clinical practice. Neurophysiology monitoring, either in the form of cortical and subcortical stimulation on awake patients, or motor evoked potentials (MEP) / somatosensory evoked potentials (SSEP) will be performed in all cases where there is an indication to do so. During neurophysiological testing, we will also apply the camera system for multispectral analysis, and record its findings in relation with the neurophysiology ones.

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

Give details of involvement, or if none please justify the absence of involvement.
We would be available to present this technology to science festivals or public debates and to discuss its implications and potential uses in a clinical environment.

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
- [x] 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
- [x] Neurological
- [ ] Oral and Gastrointestinal
- [ ] Paediatrics
- [ ] Renal and Urogenital
- [ ] Reproductive Health and Childbirth
- [ ] Respiratory
- [ ] Skin
- [ ] Stroke

Gender:	Male and female participants
Lower age limit: 18	Years Years
Upper age limit: 100	

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

We will include all adult patients under the following inclusion criteria:
• Any age
• Sex:male or female
• Candidates for surgery due to a confirmed clinical and radiological diagnosis of cranial intrinsic or an extrinsic tumour– any histological diagnosis confirming the neuro-oncological disease, including primary and secondary disease. This would include brain gliomas, meningiomas, metastasis, haemangioblastomas, pituitary adenomas, vestibular schwannomas.
• Candidates for surgery due to a confirmed clinical and radiological diagnosis of neurovascular diseases, such as brain aneurysms, occlusive arterial disease, brain vascular malformation, brain artero-venous fistula
• Agreed to take part to the present research protocol and signed the proper informed consent form

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

We willnot include patients under the following circumstances:
• Suspected differential diagnosis of other pathological condition affecting central nervous system other than the neuro-oncological or neuro-vascular disease - including demyelinating diseases, infections, brain traumas/haematomas, or auto-immune diseases
• Patients unwilling to take part in the present research protocol/failure to sign the consent form for any reason, including lack of capacity

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
Seeking consent for the procedure	1	1	10 to 45 minutes	Consent will be taken at preoperative assessment or in a private room in the admissions lounge, in clinic, or in the hospital ward by a member of the research team. Consultation can vary depending on the complexity of the clinical procedure planned.

A19. Give details of any clinical intervention(s) or procedure(s) to be received by participants as part of the research protocol. *Theseinclude usesof medicinal productsordevices,other medical treatments orassessments,mental health interventions,imaging investigationsand takingsamplesofhuman biological material. Includeprocedureswhich mightbe 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
Multispectral / hyperspectral analysis on intra-operative exposed brain / tumour tissue	1-5	0	1 to 5 minutes	This will be performed by the operating surgeon, who will be separate from the study group, as part of their standard operating practice. This will not change standard operating practice. A member of the research team will be present in the operating theatre to record the spectral data produced.

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

1 day

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.

The potential risks and burdens for research participants are minimal. Patients will experience no additional pain or discomfort as any tissue collected will be taken during standard surgical/endoscopic procedures and the patient will receive the standard level of clinical care including anaesthesia, sedation or analgesia as is appropriate.
The consent process will cause minimal inconvenience to the patient.
In the event that the clinical information required is not available in the patient's medical notes then the researcher may seek clarification on such issues as comorbidities, drug history etc from the patient themselves, however, this should take only a few minutes.
In vivo data collection will not impact on the operative procedure as the surgeon will carry out the procedure as normal and only imaging data will be collected.

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

They will contribute to developing a completely novel non-invasive technology, which can potentially reduce the number of post-operative complications and make surgery more effective at the same time.

There won't be any direct, tangible benefit from this study relevant to their care as this technique will not influence clinical decision making.

RECRUITMENT AND INFORME 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 social care or GP records, or review of medical records. Indicate whether this will be done by the direct care team orby researchers acting under arrangements with the responsible care organisation(s).*

We will seek to recruit patients undergoing elective or urgent surgery or intervention from the relevant Outpatient Clinic Department and operating theatre waiting lists. Patients with acute pathology will be identified principally from the Accident & Emergency Department and will be recruited by a clinical member of the research team. We intend to disseminate information regarding the aims and requirements of this study throughout the Trust, and this will assist further in the identification of patients suitable for study enrolment. Members of the research team will meet regularly with cancer nurse specialists and attend multidisciplinary team meetings in order to identify patients who have been diagnosed with cancer and who are scheduled to undergo surgery or intervention.

All patients enrolled in the study will be anonymised and the samples will be coded. Anonymised clinical data will be stored on Imperial College, encrypted desktop computers. Data will be anonymised by the clinical fellow, research assistant or research nurse entering the patient into the study. Coded data will be stored in a dedicated database on an encrypted Imperial College computer. Coded data will be accessed by statisticians and nonclinical researchers working on raw data. These scientists will be working for the study group at Imperial College London.
A single desktop NHS computer, that is securely encrypted will be used to store patient data relating to the study. This data will be patient identifiable. It will contain clinical data and the codes necessary to allow long-term follow up of oncological patients. Only the lead investigators will have access to this computer, and they will be responsible for entering this data. All the lead investigators of the present ethic applications are NHS Staff members and as such fully trained and committed on maintaining absolute safety of patients confidential data.

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:

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?

Elective Care: Patient recruitment
Patients will be approached in the outpatient clinic, in preassessment, or in the surgical admissions lounge. Recruitment will be performed by specialist nurses and the clinical team responsible for patient care. Patients may also be recruited by the operating surgeon.
A trained member of the research team will provide them with an information sheet and the patient will be given adequate time to consider participation prior to signing a consent form.
Acute Care: Patient recruitment
Patients admitted as an emergency will be approached in the accident and emergency department or the ward environment by members of staff within that department. Here they will be presented with an information sheet and given adequate time to consider participation before signing a consent form. Consent will be taken in private, by an adequately qualified and trained individual.

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.

Consent will be gained by the research team for all participants. Consent will be gained by a member of the research team who is properly trained.
It will be done in a place of privacy. In the case of elective surgery, patients will give consent either in the outpatient setting, in private in the admissions lounge or on the ward. Adequate time will be given to this and patients will be able to ask any questions they like. They will be provided with information sheets and access to our patient website which will be advertised in the hospital, and which will be interactive.
We will not seek informed consent from vulnerable groups.

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?

Patients will have the time from the initial consultation in the outpatient setting to their admission to hospital or between their arrival in hospital and the start of their procedure. This timeframe will vary between patients but each patient will be given adequate time to read the information sheet, discuss with relatives and ask any questions that they desire.
Patients will be able to change their mind and withdraw from the study at any time.

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?

A patient enrollment in different research studies is very unlikely to be affected by the participation on the present research protocol. Inconveniences and burdens of this study enrolment are minimal, and any results produced won't impact on clinical practice nor on other studies results in any form.

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)*
If, in the opinion of the researcher, the participant is unable to understand then they will not be recruited. However, we will adopt an interpreter in any case this is required. This will be part of the clinical consenting process, as per standard NHS policy. If the communication needs are very specific (e.g. sign language) we will not recruit patients into the study.
The hospital translation/interpreters services will be used, in line with standard NHS Code of practice/regulations, to account for patients whose first language is not English.

A35. What steps would you take if a participant, who has given informed consent, loses capacity to consent during the study? *Tick one option only.*

( ) The participant and all identifiable data or tissue collected would be withdrawn from the study. Data or tissue which is not identifiable to the research team may be retained.
(●) The participant would be withdrawn from the study. Identifiable data or tissue already collected with consent would be retained and used in the study. No further data or tissue would be collected or any other research procedures carried out on or in relation to the participant.
( ) The participant would continue to be included in the study.
( ) Not applicable – informed consent will not be sought from any participants in this research.
( ) Not applicable – it is not practicable for the research team to monitor capacity and continued capacity will be assumed.

Further details:

If you plan to retain and make further use of identifiable data/tissue following loss of capacity, you should inform participants about this when seeking their consent initially.

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
- [ ] Electronic transfer by magnetic or optical media, email or computer networks
- [ ] 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
- [x] Use of audio/visual recording devices
- [x] Storage of personal data on any of the following:
  - [ ] Manual files (includes paper or film)
  - [x] NHS computers
  - [ ] Social Care Service computers
  - [ ] Home or other personal computers
  - [x] University computers
  - [ ] Private company computers
  - [x] Laptop computers

Further details:
During intraoperative multispectral data collection, anonymous video recording will be carried out in order to sync spectral data collected with the surgical procedure. This information will non-identifiable and coded, in keeping with the previously described methods. As mentioned, all biological data will be coded and anonymised for storage on encrypted Imperial College computers. However, a single NHS encrypted computer will be used to store the original patient details and corresponding codes so that oncological patients can be followed up.

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

As mentioned, all biological data will be coded and anonymised for storage on encrypted Imperial College computers. However, a single NHS encrypted computer will be used to store the original patient details and corresponding codes so that oncological patients can be followed up. The profile of the NHS Trust computer is fully encrypted and regulated by Imperial College NHS Trust policy.

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.*

All personal data will be fully anonymised. Each patient will be given a specific code for the type of tissue collected and the timing of collection.
Confidentiality will be ensured by preventing access to personal data in keeping with the policy of Imperial College NHS trust. Study participants will not be permitted to remove any personal data from the NHS Trust building at Charing Cross Hospital. Only anonymised, coded data will be released for analysis by the study group.

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.*

Key members of the research team ([NAME] and [NAME]) will have access to the patient's medical records in order to record relevant clinical information. The information will be stored under the patient's research code which will not be identifiable. The patient information sheet and consent form will include this information and the patient's consent for this will be sought.

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?

Data generated from the study will be analysed by the [TEAM] team at Hamlyn Centre at Imperial College of London. Sites are in South Kensington Campus and St. Mary's Hospital Campus. All patients data will be anonymized and assigned to a study protocol number. Only fully anonymized data will be provided.

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

Title Forename/Initials Surname	[TITLE] [FORENAME] [SURNAME]
Post	Neurosurgery Research Fellow, PhD Student
Qualifications	Medical Doctor, FEBNS (Fellow of the European Board of Neurosurgery), CCT in Neurosurgery (Italy)
Work Address	Fulham Palace Rd, Hammersmith
Post Code	W68RF
Work Email	[EMAIL]
Work Telephone	[TELEPHONE]
Fax	[FAX]

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:
All data will be archived for a period of 5 years. We will store personal data in keeping with the Imperial College policy on retention of research data. This will ensure that we are able to follow oncology patients up for the duration of their clinical care, though this follows up period rarely exceeds five years.

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

Years: 5
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.*

All data will be accessed by the PI and his co-investigator. Details about how to ensure security are already provided above: all NHS and College computers will be encrypted, and no identifiable personal data will be stored. After the 5 years period, data will be erased, unless results show that further studies are indicated. In that case, we will amend the present application to request extension.

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.

PUBLICATION AND DISSEMINATION

A50-1. Will the research be registered on a public database?

The UK Policy Framework for Health and Social Care Research sets out the principle of making information about research publicly available. 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.
As this is a pilot study, we are not planning to register it as a clinical trial at this stage. However, if results will encourage further clinical validation, we will definitively consider registration to www.clinicaltrial.org

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

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

☑ Peer reviewed scientific journals

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

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

We are not planning to use any identifiable personal data. As explained above, we will assign clinical data to a protocol number, and all useful clinical data will be stored under that protocol number.

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.
We will not inform individual participants. However, published data will be available to the public, and participants will be able to contact one of the researchers should they wish to know the outcome.

5. Scientific and Statistical Review

A54-1. How has the scientific quality of the research been assessed?*Tick as appropriate:*

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

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:*

- [ ] Review by independent statistician commissioned by funder or sponsor
- [ ] Other review by independent statistician
- [ ] Review by company statistician
- [x] Review by a statistician within the Chief Investigator’s institution
- [ ] Review by a statistician within the research team or multi−centre group

☐ Review by educational supervisor

☑ 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

Department
Institution
Work Address

Post Code
Telephone
Fax
Mobile
E-mail

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

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

Todetermine whether the multispectral/hyperspectral analysis is a potential tool to be used in neurosurgical clinical practice to identify tumour tissue VS normal brain, to delineate eloquent/functional brain areas, and to identify areas of hypoperfusion during neurovascular procedures.

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

Is multispectral/hyperspectral analysis comparable with current neurophysiological, microscopic, and neurovascular techniques to identify differences in tissue perfusion during brain surgery?

Can multispectral/hyperspectral analysis be useful in combination with standard fluorescence techniques during neuro-oncological and neuro-vascular procedures?

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:200 Total international sample size (including UK):200 Total in European Economic Area:0

Further details:
We will collect spectral data up until the statistical model used for multivariate analysis does not longer improve the degree of accuracy.
Figueroa RL, Zeng-Treitler Q, Kandula S, Ngo LH. Predicting the sample size required for classification performance. BMC Med Inform Decis Mak. 2012 Feb 15;12:8.
However, we will aim to recruit approximately 50 patients in 4 separate cohorts. We approximate that 200 patients will provide a spectral database of 5.000-10.000 spectra which we calculate is adequate for diagnostic validation purposes.

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.

We did not use a formal sample size calculation, but as above predictive models suggest that reliable statistical results can be achieved once the model no longer improves the accuracy.

A61-1. 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.

We will run parametric tests on our population of patients to make sure that the sample is homogeneous and consistent with the other literature series reporting similar diseases.

We will compare the signal in one region of the tumour to a neighboring 'healthy' region. The signal itself will come from a processed set of images of the brain, where we will fit the data using one of our established models to extract an indication of tissue oxygenation (as a %) on a per-pixel basis. We will also compare the differences in signals in awake patients, before, during, and after the execution of a task, to evaluate whether there is a statistically significant difference between the signal before and after any intra-operative stimulation.

Each image set will be analysed separately because there will be variability between patients and we will not be able to fully account for this with the limited number of datasets that we are going to record (a well-known problem with many biophotonics/optical techniques). This will all be done offline after the surgery is complete, with a primary aim is to observe whether the technique is capable of detecting changes in the tissue.

Regarding the UV and IR fluorescence signal, we will evaluate whether multispectral/hyperspectral imaging can increase the distinction of the fluorophore signal compared with the background. Dedicated statistical software will be used for this analysis.

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	[TITLE] [FORENAME] [SURNAME]
Post Qualifications	
Employer	Imperial College of London
Work Address	415 Bessemer Building, South Kensington Campus
Post Code	SW7 2AZ
Telephone	[TELEPHONE]
Fax	[FAX]
Mobile	[MOBILE]
Work Email	[EMAIL]

A64. Details of research sponsor(s)

A64-1. Sponsor

Lead Sponsor

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:

If Other, please specify:

Contact person

Name of organisation	Imperial College NHS Trust
Given name	[FORENAME]
Family name	[SURNAME]
Address Town/city Post code	Joint Research Office Room 221 Medical School Building, St Marys Campus, Norfolk Place London W2 1PG
Country	UNITED KINGDOM
Telephone	[TELEPHONE]
Fax	[FAX]
E-mail	[EMAIL]

A65. Has external funding for the research been secured?

Please tick at least one check box.

- [ ] Funding secured from one or more funders
- [x] 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	[ORGANISATION]
Address	Chalkdell Drive Suite 3, Shenley Pavilions Milton Keynes MK5 6LB 01908
Post Code	867200
Telephone	
Fax	
Mobile	
Email	[EMAIL]

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

Amount: 20.000

Duration
Years: 2
Months:

If applicable, please specify the programme/ funding stream:

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

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

( ) Yes (•) No

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

( ) Yes (•) No

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

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

Title Forename/Initials Surname

[TITLE] [FORENAME] [SURNAME]

Organisation	Joint Research Compliance Office Imperial College of London
Address	Norfolk Place Room 221, Medical School Building, St Marys Campus
Post Code	W2 1PG
Work Email	[EMAIL]
Telephone	[TELEPHONE]
Fax	[FAX]
Mobile	[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:

North West London

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

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

Planned start date:04/04/2019
Planned end date:04/04/2024
Total duration:
Years:5 Months:0 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

The end of the trial will be defined by a 95% diagnostic sensitivity and specificity of the technique using intra-operative neuro-stimulation and histopathology as a gold standard.

A71-1. Is this study?

- (●) Single centre
- ( ) Multicentre

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

- [x] England
- [ ] Scotland
- [ ] Wales
- [ ] Northern Ireland
- [ ] Other countries in European Economic Area

Total UK sites in study

Does this trial involve countries outside the EU?

( ) Yes (●) No

A72.WhichorganisationsintheUKwill host the research? *Please indicate the type of organisation by ticking the box and give approximate numbers if known:*

- [x] NHS organisations in England 2
- [ ] NHS organisations in Wales
- [ ] NHS organisations in Scotland
- [ ] 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: 2

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

○ Yes ◉ No

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? *Pleasetick box(es) asapplicable.*

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)

Imperial College of London will provide insurance and indemnity

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)

Imperial College of London will provide insurance and indemnity

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.

- [x] 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.

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

- (•) Yes
- ( ) No
- ( ) Not sure

A79.Please select the level of commercial participation in this project.

- (•) None
- ( ) Industry funding, but not industry sponsored
- ( ) Industry funding and industry sponsored
- ( ) Industry sponsored, but not industry funded

A80.Please select the main subject area of research. dditional sub-topics may be selected, if required

- [ ] Age and Ageing
- [ ] Anaesthetics
- [x] Cancer (includes malignant haematology
- [x] Cardiovascular
- [ ] Clinical
- [ ] Critical Care
- [ ] Dementias and Neurodegenerative Diseases
- [ ] Dermatology
- [ ] Diabetes
- [ ] Ear, Nose and Throat
- [ ] Gastrointestinal
- [ ] Genetics
- [ ] Health Services Research
- [ ] Hepatology
- [ ] Immunology and Inflammation
- [ ] Infectious Disease and Microbiology
- [ ] Injuries and Accidents

- [ ] Medicines for Children (does not include Paediatrics)
- [ ] Mental Health
- [ ] Metabolic and Endocrine
- [ ] Musculoskeletal (Rheumatoid Arthritis is a separate category)
- [x] Nervous System Disorders
- [ ] Non-malignant Haematology
- [ ] Ophthalmology
- [ ] Oral and Dental
- [ ] Paediatrics (does not include Medicines for Children)
- [ ] Primary Care
- [ ] Public Health Research
- [ ] Renal
- [ ] Reproductive Health and Childbirth
- [ ] Respiratory
- [ ] Rheumatoid Arthritis
- [ ] Stroke
- [x] Surgery
- [ ] Urogenital

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?

Brain tissue (oncological and not oncological), meninges, blood samples, skin, connective tissue (such as muscles, ligaments, bone), blood vessels, cartilage

2.Will the samples be released to the researcher:

Infully 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.

Consent has been provided from all patients prior to submission of samples to the Imperial College Tissue Bank.

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?

We will perform in vivo analysis on samples. This analysis will consist in imaging acquisition, and won't cause any direct or indirect damage or modification to the analyzed tissue. Human tissues will be collected only in the context of the clinical diagnostic process. This will be performed by a dedicated histopathologist. Data obtained for histological diagnosis will be used for cross-validation of intra-operative findings.

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

Name of the research tissue bank (or other collection):
Imperial College Healthcare Tissue Bank

Does the bank/collection hold a licence from the Human Tissue Authority to store tissue for research?

◉ Yes ○ No

REC reference no. (if the bank/collection is ethically approved):
[REFERENCE NUMBER]

Details of organisation with responsibility for the bank/collection:

Organisation: Imperial College

Title Forename/Initials Surname

Address

Post Code
Telephone
Fax
Mobile
Email
Contact point

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.

Samples obtained at Charing Cross Hospital will be stored in a locked freezer and/or in paraffin blocks in the histopathology facility, Charing Cross Hospital, 3rd floor.

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:

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?

Not planning to use newly obtained tissue or other human biological materials for research purposes at this stage.

2. Who will collect the samples?

N/A

3. Who will the samples be removed from?

☐ Living donors

☐ The deceased

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]*

Infully anonymised form? *(link to donor broken)*

○ Yes ◉ No

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

○ Yes ◉ No

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

○ Yes ◉ No

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

N/A

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

If No, please justify. If Yes, say what arrangements will be made and give details of the support or counselling service.

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

N/A

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

☐ Transfer to research tissue bank

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

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

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

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

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

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

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

☐ Other

☐ Not yet known

Please give further details of the proposed arrangements:

PART C: Overview of research sites

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

Investigator identifier	Research site		Investigator Name	
IN1	○ NHS/HSC Site ◉ Non-NHS/HSC Site		Forename Middle name Family name Email Qualification (MD...)	[FORNAME] [SURNAME] [EMAIL] [QUALIFICATIONS]
	Institution name	Imperial College NHS Trust, Charing Cross Hospital		
	Department name	Neuroscience, Neurosurgery	Country	UNITED KINGDOM
	Street address	Fulham Palace Road		
	Town/city	London		
	Post Code	W6 8RF		
	Country	UNITED KINGDOM		