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)
Guiding Light Optimising Wide local excisions (GLOW)

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)*

- [x] 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?

- [x] 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

Please describe briefly the involvement of the student(s):
The PhD student will be responsible for organizing IRAS approval (this includes creating protocols/ information sheets/ consent forms, etc.), recruiting patients, consenting patients, collecting and analysing the data, publishing the data.

9a. Is the project being undertaken in part fulfilment of a PhD or other doctorate?

◉ 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

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

REC Name:
London - Surrey Research Ethics Committee

RECReference Number:
[REF]

Submission date:
07/05/2019

PART A: Core study information

1. ADMINISTRATIVE DETAILS

A1.Full title of the research:

The Use of Fluorophores Intraoperatively for Tumour Detection in Breast Cancer Surgery

A2-1. Educational projects

Name and contact details of student(s):

Student 1

Title Forename/Initials Surname	[TITLE] [FORENAME] [SURNAME]
Address	3rd floor, Patterson building S Wharf Rd, Paddington
Post Code	W2 1PF
E-mail	[EMAIL]
Telephone	[TELEPHONE]
Fax	[FAX]

Give details of the educational course or degree for which this research is being undertaken:

Name and level of course/ degree:
PhD in Clinical Medicine Research (Surgery and Cancer)-full time

Name of educational establishment:
Imperial College London

Student 2

Title Forename/Initials Surname	[TITLE] [FORENAME] [SURNAME]
Address	Hamlyn Centre for Robotic Surgery Imperial College London Exhibition Road, Bessemer Building
Post Code	SW72AZ
E-mail	[EMAIL]
Telephone	[TELEPHONE]
Fax	[FAX]

Give details of the educational course or degree for which this research is being undertaken:

Name and level of course/ degree:
PhD in Clinical Medicine Research (Surgery and Cancer)-full time

Name of educational establishment:
Imperial College London

Name and contact details of academic supervisor(s):

Academic supervisor 1

Forename/Initials Surname	[TITLE] [FORENAME] [SURNAME]
Address	Hamlyn Centre 415 Bessemer Building Exhibition Road
Post Code	SW7 2AZ
E-mail	[EMAIL]
Telephone	[TELEPHONE]
Fax	[FAX]

Please state which academic supervisor(s) has responsibility for which student(s):
Please click"Save now"beforecompletingthistable.Thiswillensurethatallofthestudent and academic supervisor details are shown correctly.

Student(s)		Academic supervisor(s)
Student 1	[TITLE] [FORENAME] [SURNAME]	☑ [TITLE] [FORENAME] [SURNAME]
Student 2	[TITLE] [FORENAME] [SURNAME]	☑ [TITLE] [FORENAME] [SURNAME]

A copy of a current CV for the student and the academic supervisor (maximum 2 pages of A4) must be submitted with the application.

A2-2. Who will act as Chief Investigator for this study?

- ○ Student
- ○ Academic supervisor
- ◉ Other

A3-1. Chief Investigator:

Title Forename/Initials Surname	[TITLE] [FORENAME] [SURNAME]
Post	Oncoplastic Breast Surgeon, Reader in Breast Surgery
Qualifications	MBBS, FRCS, Master of Surgery, PhD
ORCID ID	[ORCID ID]
Employer	Imperial College London
Work Address	Queen Elizabeth the Queen Mother Wing (QEQM), S Wharf Rd London
Post Code	W2 1NY
Work E-mail	[EMAIL]
* Personal E-mail	[EMAIL]
Work Telephone	[TELEPHONE]
Fax	0000

** 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	Room 221, level 2 Medical School Building Norfolk Place
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:	GLOW1 1
Protocol Version:	24/04/2019
Protocol Date:	
Funder's reference number (enter the reference number or state not applicable):	[REFERENCE]
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.
This study is linked to another study called Real time tissue validation using NIR fluorescence imaging: Surgery. The camera system developed and tested during that study will be used to quantify fluorescence in this study.
Study details are as follows:
Applicant's/organisation's own reference number: NQHAM_P48517
Sponsor's/protocol number: NA
Protocol Version: 1 Protocol Date: 31/05/2018
Funder's reference number: II-LB-0214-20009
Project website: http://ubimon.doc.ic.ac.uk/elsonds/m765.html

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.*

Approximately 1 in 5 women undergoing breast conserving surgery for cancer will have tumor left behind after resection, thus needing further surgery. This is problematic in terms of the extra stress put upon the patient of having to undergo further surgery, poorer cosmetic outcome, the delay in chemoradiotherapy, as well as the cost to the NHS and the economy.

This pilot study aims to develop technology to detect the difference between healthy and breast cancer tissue, using various contrast agents (fluorophores) and a multispectral imaging system. The fluorophores are designed to target breast cancers through various proteins or metabolic pathways. The multispectral imaging system will then be able to activate the fluorophores and detect their signal, thus allowing the cancer can be seen simultaneously. By being able to show the surgeon the tumour at the same time he is operating, there is the potential that he will be able to cut it all out at the first operation.

The fluorophores we plan on using to investigate breast cancer are: aminolevulinic acid (ALA) & EMI-137.
ALA is an amino acid which naturally occurs in the body. It is a substrate for protoporphorin IX (PpIX), an endogenous fluorophore. ALA is currently approved for use in brain, bladder, and skin cancer operations in Europe.
EMI-137 is a protein which targets the C-met receptor. It is currently being explored for its usefulness in various cancers.
Side effects are minimal (nausea, headache, etc.) & uncommon with all dyes.

The use of this imaging system could guide surgeons in real time and thus improve surgery outcomes and decrease recurrence rates.

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.

The purpose of the current clinical study is to trial various fluorophores using an optical imaging system to visualise cancerous tissue. The overall objective of this study is to guide surgeons in real time and improve outcomes for patients. This is an unmet clinical need since, to date, there is no standard imaging approach for real time intraoperative guidance for tumour resection. In this study, the fluorophores being investigated are EMI 137 & ALA. All fluorophores will be administered at a dose well below toxicity level. EMI 137 will be administered intravenously with a 0.13mg/kg dose. ALA will be administered orally with a 20mg/kg dose. All of these doses are well below toxicity level. To date, only mild adverse events have been reported (nausea, headache, oral pruritus, etc.), however these are uncommon (1/100-1/1000 event rate). There have been no cases reported of anaphylaxis with use of these agents, however surgical teams will be ready to immediately administer epinephrine/ antihistamines/ corticosteroids if such reactions were to occur. The patients will be under general anaesthesia and hence be fully monitored. Any change in physiological parameters will be detected by the Anaesthetist and managed accordingly. A camera system will be used to acquire simultaneous standard white light and NIR images intraoperatively, using imaging optics located appropriately, depending on the desirable field of view. This proposed test does not in any way interfere with the primary procedure, and will not be used as a guidance tool to improve on-table decision making regarding the adequacy of excision margins in this study. If the image quality and correspondence with pathology is found to be acceptable, then in future studies images may inform the need for further immediate shave excision. It is estimated that this process will add a maximum of 15 minutes to the normal procedure and the acquired images will be evaluated off-line by clinical and technical members of the research team. The results of the study will be used to compare the visualisation of the region of interest with both the visible and NIR set up. Surgeons will be asked to qualitatively compare the different images in a blinded test post-operatively, and quantitative information will also be acquired about image brightness and contrast.

Multispectral/ fluorescence imaging is non-contact and uses only the standard surgical light illumination or the Xenon light source (MAX-303, Asahi Spectra). During surgery it will be used at the same time as the other proposed imaging modalities, therefore it is not expected that it will add any significant time to the procedure.

These procedures will be done in a controlled theatre setting by [NAME], Consultant in Oncoplastic Breast Surgery, Breast Unit, Imperial College Healthcare NHS Trust, [NAME], Consultant Plastic and Reconstructive Surgeon and [NAME], Consultant Oncoplastic Breast Surgeon, at Imperial College NHS Trust. The cases will be derived from a suitable cohort of their own patients. These breast conserving surgeries are performed routinely for breast cancer as part of their practice. An invitation to partake in the study will be sent alongside patient information leaflet in conjunction with letters informing patients about their admission details for surgery. Patients considering taking part in the study will be seen by [NAME] / [NAME] / [NAME] who will explain and discuss the study with them. Up to 2 weeks' time will be given for the patients to process the information and take a decision. During this time, patients will be able to contact the research team for further information. Contact details will be provided in the patient information sheet. The Informed consent will be sought from patients who fulfil the inclusion criteria admitted in the morning of the operation. At the same time, [NAME] / [NAME] / [NAME] or a member of the clinical team with knowledge of the protocol will re-explain and re-discuss the contents of the patient information sheet.

Patient data will be coded and anonymised (using only trial numbers) in the results section of data collection, and no names or hospital numbers will be used in conjunction with the data. The data stored will be in a password protected and encrypted in a SafeStick USB memory stick.

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)
- ☐

This study will be a single centre prospective cohort feasibility/ pilot study.

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

The principal objective of this research is to develop a technology which can distinguish between cancerous tissue and normal tissue in real time, using various fluorescent dyes in combination with a specially designed camera system.

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

The secondary objective of this research is to determine whether this technology is able to provide a sufficient visual cue to the surgeon to determine whether or not further cancer resection would need to be undertaken.

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

Approximately 1 in 5 women undergoing Breast Conserving Surgery (BCS) for cancer require a re-operation since not all the tumour was removed (1-5). Any tumour left behind more than doubles the chance of the cancer coming back (6). The risk of the cancer returning is not removed by the use of radiotherapy, systemic chemotherapy or hormone therapy (7). Having to undergo a second operation can cause patient anxiety, impaired cosmetic outcome (8), wound complications (9), a delay in associated therapy (chemotherapy and radiotherapy) (10), and increases costs for the hospital and society. A study done in the USA calculated that performing these repeat operations costs approximately $18.8 million per year (11).
As this is an obvious problem, there are many technologies which are trying to prevent leaving any cancer tissue behind. Examination of removed tissue under the microscope (like frozen section and cytology), are accurate (12) and may reduce re-operation rates (13, 14), but the techniques are slow and labour intensive and do not actually guide the operation in real time. Presently, there is little in the way of image guidance technology which works in real-time. Indeed, the main operative planning of the resection relies on the surgeons' judgment and tactile skills, hence the high rates of close/ positive margins following BCS. Localisation techniques such as placement of a wire in the breast with its tip indicating the cancer site are only able to provide crude co-ordinates of cancers for impalpable tumours. What is required is a system that helps the surgeon better see the difference between cancer and normal breast tissues immediately during the operation to better plan the extent of tumour removal.
Therefore, the scientific justification of this project is based on the advantages of fluorescence imaging to detect the subtle differences between healthy and cancerous tissues during breast conserving surgery and provide immediate visual cues. This simple illumination and imaging system are designed based on the cancer targeted fluorescence of ALA & EMI-137; and will provide real time images of the cancer. The imaging system measures how brightly those dyes glow, and is able to display this information immediately to the surgeon, who can then make informed surgical decisions on where to cut.
ALA (aminolevulinic acid) is an amino acid which naturally occurs in the body. In cancer cells, taking ALA causes an

accumulation of protoporphorin IX (a naturally occurring fluorophore) due to abnormal metabolism. ALA is currently approved by the European Medicines Agency for oral intraoperative use in brain tumour resections as well as topical use in bladder and skin cancers (15). EMI-137 is an amino acid chain connected to a fluorescent dye. It targets the C-met receptor protein, present in the extracellular membranes of cells. C-met can be overexpressed in up to 70% of breast cancers (16), and is linked to breast cancer severity (17-19). It is currently being explored for its usefulness in colorectal cancer, breast cancer, orofacial malignancies, and Barret's esophagus. The imaging system will use one of those targeted dyes listed above in conjunction with a special camera system that is able to count how bright those dyes glow in the cancer. That information will then be and transformed into a picture which can be shown on a screen in the operating theatre, allowing the surgeon to see where the cancer is and enable them to cut it all out. References: (1) Wilke LG, Czechura T, Wang C, Lapin B, Liederbach E, Winchester DP, et al. Repeat surgery after breast conservation for the treatment of stage 0 to II breast carcinoma: a report from the National Cancer Data Base, 20042010. JAMA Surg 2014 Dec;149(12):1296-1305. (2) Landercasper J, Whitacre E, Degnim AC, Al-Hamadani M. Reasons for re-excision after lumpectomy for breast cancer: insight from the American Society of Breast Surgeons Mastery(SM) database. Ann Surg Oncol 2014 Oct; 21(10):3185-3191. (3) McCahill LE, Single RM, Aiello Bowles EJ, Feigelson HS, James TA, Barney T, et al. Variability in reexcision following breast conservation surgery. JAMA 2012 Feb 1;307(5):467-475. (4) Jeevan R, Cromwell DA, Trivella M, Lawrence G, Kearins O, Pereira J, et al. Reoperation rates after breast conserving surgery for breast cancer among women in England: retrospective study of hospital episode statistics. BMJ 2012 Jul 12;345:e4505. (5) Isaacs AJ, Gemignani ML, Pusic A, Sedrakyan A. Association of Breast Conservation Surgery for Cancer With 90Day Reoperation Rates in New York State. JAMA Surg 2016 Jul 1;151(7):648-655. (6) Houssami N, Macaskill P, Marinovich ML, Morrow M. The association of surgical margins and local recurrence in women with early-stage invasive breast cancer treated with breast-conserving therapy: a meta-analysis. Ann Surg Oncol 2014 Mar;21(3):717-730. (7) Moran MS, Schnitt SJ, Giuliano AE, Harris JR, Khan SA, Horton J, et al. Society of Surgical Oncology–American Society for Radiation Oncology Consensus Guideline on Margins for Breast-Conserving Surgery With Whole-Breast Irradiation in Stages I and II Invasive Breast Cancer. JCO 2014 05/10; 2017/08;32(14):1507-1515. (8) Heil J, Breitkreuz K, Golatta M, Czink E, Dahlkamp J, Rom J, et al. Do reexcisions impair aesthetic outcome in breast conservation surgery? Exploratory analysis of a prospective cohort study. Ann Surg Oncol 2012 Feb; 19(2):541547. (9) Xue DQ, Qian C, Yang L, Wang XF. Risk factors for surgical site infections after breast surgery: a systematic review and meta-analysis. Eur J Surg Oncol 2012 May;38(5):375-381. (10) Kouzminova NB, Aggarwal S, Aggarwal A, Allo MD, Lin AY. Impact of initial surgical margins and residual cancer upon re-excision on outcome of patients with localized breast cancer. Am J Surg 2009 Dec;198(6):771-780. (11) Abe SE, Hill JS, Han Y, Walsh K, Symanowski JT, Hadzikadic-Gusic L, et al. Margin re-excision and local recurrence in invasive breast cancer: A cost analysis using a decision tree model. J Surg Oncol 2015;112(4):443-448. (12) St John ER, Al-Khudairi R, Ashrafian H, Athanasiou T, Takats Z, Hadjiminas DJ, et al. Diagnostic Accuracy of Intraoperative Techniques for Margin Assessment in Breast Cancer Surgery: A Meta-analysis. Ann Surg 2017 Feb; 265(2):300-310. (13) Butler-Henderson K, Lee AH, Price RI, Waring K. Intraoperative assessment of margins in breast conserving therapy: a systematic review. Breast 2014 Apr;23(2):112-119. (14) Esbona K, Li Z, Wilke LG. Intraoperative imprint cytology and frozen section pathology for margin assessment in breast conservation surgery: a systematic review. Ann Surg Oncol 2012 Oct;19(10):3236-3245. (15) Krammer B, Plaetzer K. ALA and its clinical impact from benchside to bedside. Photochem Photobiol Sci. 2008;7:283-9. (16) Rhagav K, Wang W, Liu S, Chavez-MacGregor M, Meng X, Hortobagyi G, et al. cMET and phospho-cMET protein levels in breast cancers and survival outcome. Clin Cancer Res. 2012;18. (17) Garcia S, Dales JP, Jacquemier J, Charafe-Jauffret E, Birnbaum D, Andrac-Meyer L, et al. c-Met overexpression in inflammatory breast carcinomas: automated quantification on tissue microarrays. Br J Cancer. 2007;96(2):329-35. (18) Edakuni G, Sasatomi E, Satoh T, Tokunaga O, Miyazaki K. Expression of Hepatocyte Growth Factor/ C-Met pathway is increased at the cancer front in breast carcinoma. Pathology International. 2001;51:172-8. (19) Yamashita J, Ogawa M, Yamashita S, Normua K, Kuramoto M, Saishoji T, et al. Immunoreactive Hepatocyte Growth Factor is a strong and independent predictor of recurrence and survival in human Breast Cancer. Cancer Research. 1994;54:1630-3.

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 patients who conform to the inclusion criteria will be approached by the operating surgeon/the project CI

([NAME]) or a clinical member of the research team. This will either happen during their initial outpatient surgical appointment where they discuss the operation, anaesthetic pre-assessment clinic, during the breast care nurse specialist meetings on wide local excisions, or over the telephone. [NAME] or a clinical member of the research team will explain the rationale behind the study, the reason for the administration of the fluorophore (either ALA or EMI-137), the fluorescence imaging procedure and the use of the LED light source with the aid of the patient information leaflet. It will be explained that the study will add only approximately 15 minutes to the primary procedure being done, and no additional samples (above those deemed necessary for the primary procedure) would be taken. The risk(s) of the procedure will also be explained in detail. Finally, the patient will be informed that the study will be done under strict anonymity conditions and the patient's names or hospital numbers will not be stored. However, images and videos will be stored, anonymously. The data and recordings will be linked anonymised and encrypted. It will be made clear that they have the right to withdraw consent and thus their participation in the study at any time without the need to give a reason and without any effects on the standard of care they will receive. Patients will have had time to consider and read about the study at least two weeks prior to the intervention date. During this time, patients will be able to contact the research team for further information. Contact details will be provided in the patient information sheet. The Informed consent will be sought from patients who fulfil the inclusion criteria admitted in the morning of the operation. Having read the document and having had time to assimilate its information and ask questions, if in agreement, the patient will sign one consent form for the study and another for their primary procedure and re-discuss the contents of the patient information sheet. One copy of their consent form will be kept in their medical records. The patients will retain the patient information leaflet. While in the day case surgery unit, the patients will receive either: a) A 0.13 mg/kg dose of EMI 137, prepared & cross-checked by a nurse, then injected intravenously into the patient at least 3h prior to their operation. b) A 20mg/kg dose of ALA, prepared by a doctor and cross-checked by a nurse, and taken orally by the patient 3-6h prior to their operation. The surgery will be performed by a Consultant Surgeon with knowledge of the protocol under the supervision of [NAME] / [NAME] / [NAME]. The operation (Breast Conserving Surgery) will be undertaken in theatre, where standard general anaesthesia (drug induced loss of sensation/consciousness) will be given. Once surgical excision of the specimen (tumour) has occurred, a series of images will be taken to record the magnitude of tissue fluorescence around the tumour specimen (tissue that has been excised-removed) and in the resection cavity (surgical bed). In order to evaluate and assess the tumour and its boundaries, the fluorescence and multispectral images acquired during the surgery will be reviewed off-line by [STUDY TEAM NAMES]. The patient will then be recovered as standard post-operative care and transferred to the ward. Prior to discharge the patient will be reviewed by the clinician to ensure that everything has progressed smoothly and there are no concerns from either the patient's or clinician's perspective. All patient data accrued from the study will be linked anonymised (using only trial numbers) and stored encrypted in a USB memory stick (SafeStick).

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.
he Imperial CRUK patient and public involvement PPI group, facilitated by [NAME] (via the Imperial College Academic Health Science Centre) was involved in the design of the research, management of the research and dissemination of findings. Both patient information sheet and consent form has been iteratively developed with feedback from the patient and public involvement PPI group that advised mostly on vocabulary choice and risk assessment and management. Emails containing the forms have been sent out to consenting members of the public for rapid feedback. Additionally, [NAME] and [NAME] explained the summary of the Project to the PPI group meetings on 6/3/19 & 14/03/2019. Suggestions from the group about how the summary of the study findings sheets were taken into consideration. The same group will be contacted at a later stage (dissemination of findings stage) to advise on wording and sheet layout. Having understood the importance of the study’s questions and its potential benefits to patients, hospital, and society, the group was consulted on the

feasibility of the study and acceptance level of its associated risks. To manage risks considered as low by the panel, appropriate controls were identified. We finalized patient exclusion criteria based on risks considered as not acceptable by the group.

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: Female participants only

Lower age limit: 40 Years Years

Upper age limit: 80

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

Adult female patients undergoing breast-conserving surgery for cancer
Gender: Female Age range: Adult (40 to 80) Clinical condition: breast cancer

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

Gender: Male
Age range: outside inclusion criteria: <40 or >80
Pregnant or lactating women
Patients known to be allergic to dyes or contrast agents
Patients in renal failure/uremia/on dialysis
Patients in liver failure
Patients in cardiac failure
Patients with porphyria (only applicable in ALA trial).
Patients taking nephrotoxic/ hepatotoxic/ phototoxic medications
Patients who are unable to or refuse to give consent
Patients who withdraw consent
Patients in whom delay to obtain optical images is deemed inappropriate (e.g. patients at high risk needing rapid surgery)

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	15	4 Surgeon & assistants in Charing Cross Hospital.
Provision of patient information sheet	1	0	min	10	Surgeon & assistants in Charing Cross Hospital.
Informed consent	1	0	min		

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 5 min	4
Administration of fluorophore (either oral ALA or injection of EMI 137) & ondansetron (if oral ALA preparation being taken)	1	0	5 min	Surgeon and assistants in Charing Cross Day Surgery Unit
Multispectral imaging	1	0		Surgeon and assistants, in Charing Cross operating theatres.
NIR fluorescence imaging	1	0	5 min	Surgeon and assistants, in Charing Cross operating theatres.

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

Eachparticipant will be in the study from the point of obtaining consent until the operation concludes (total of a few hours). There are no post-operative interventions.

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 ALA formulation which will be used in this study is the oral preparation called Gliolan, which has been approved by the European Medical Council for use in fluorescence guided brain surgery. The by-products undergo hepatic and renal clearance, and is advised to be used to be used with caution in those with liver impairment, renal impairment, and avoided in patients with porphyria (patients with these comorbidities will be excluded from the study). Active substance side effects are uncommon (1/100- 1/1000) but can include hypotension, nausea, photosensitivity reaction, photodermatosis. Patients should avoid strong light sources for 24h after administration and will be given appropriate sun protection (sun block). No cases of anaphylaxis have been reported to date. There have been some limited animal studies which suggest an embryotoxic activity of 5-ALA plus light exposure (but no studies regarding breast-feeding), thus pregnant and breast-feeding patients will be excluded from the study. No compatibility studies with food or other medications, although it is advised to avoid phototoxic/ hepatotoxic medications. However, as all patients will be on an empty stomach prior to anaesthesia, thus should not be affected.
EMI-137 is an amino acid chain combined with a fluorescent cyanine. Toxicity studies done in animals found no toxicity even at estimated maximal efficacy dose as a single (111.6mg/kg) or multiple repeated doses (16.8mg/kg), which is much higher than the dose which will be used in our study (0.13mg/kg). Single intravenous administration of EMI-137 Injection at doses of 0.02-0.18 mg/kg was well tolerated and safe in male and female healthy volunteers. Side effects deemed treatment related included headache, somnolence, dizziness, and skin discoloration. EMI137 Injection did not cause any clinically significant adverse events or death or lead to clinically significant changes in symptoms, blood and urinary laboratory parameters, vital signs or ECG variables. No cases of anaphylaxis have been reported to date. EMI 137 is excreted primarily via renal clearance although some can be excreted via hepatic clearance, thus patients with renal or hepatic impairment will be excluded from the study. To date, it is not known whether EMI 137 can cause foetal harm when administered to a pregnant woman or if EMI 137 is excreted in human milk, thus pregnant or breast-feeding patients will be excluded.
The risks outline above are outweighed by the importance of fluorophore exploitation, which is fundamental for the purposes of this study. There are no other clinically approved fluorophore agents since for breast surgery, thus there is no alternative at present. Surgical teams will be ready to immediately administer epinephrine/ antihistamines/ corticosteroids if any severe adverse reactions such as anaphylaxis occur. The patients will be under general anaesthesia and hence fully monitored. Any change in physiological parameters will be detected by the Anaesthetist and managed accordingly.

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

Research participants will have the opportunity to engage with cutting edge research in surgical technology, thus contributing to evidence based medicine.

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 searchofGP records,orreviewof medicalrecords. Indicate whether thiswillbe doneby thedirect healthcareteamorby researchers actingunder arrangements with the responsible care organisation(s).*

Potentially eligible patients will be identified at a multi-disciplinary team cancer meeting held at Imperial College Healthcare NHS Trust, (MDTs that [NAME] / [NAME] / [NAME] attend). We have applied for Experimental Cancer Medicine Centre (ECMC) / Imperial Cancer Biomarker Resource Centre (ICBRC) support inclusive of the surgical trials practitioner who will also attend MDT's and help identify & recruit patients. The ECMC nurse has license to attend at Imperial College Healthcare Trust from 11.2.19-10.2.22 in the purpose of a clinical trial practitioner. The patients included will be those who fall under the care of [NAME] / [NAME] / [NAME].

Their notes and previous investigations would have been checked by the clinical, radiology and pathology team prior to making a consideration as to their suitability for this study.

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:
Patient's hospital notes will be reviewed as part of the information gathering aspect of the study and to collect information about their pathology and stage of their disease and to confirm the eligibility criteria for the study.

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 whatstepshave beenor willbe takento informpatients and service usersofthe potentialuseof theirrecordsfor thispurpose.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.*

The confidentiality issue will be explained to the patient during the discussion with [NAME] / [NAME] / [NAME], as well as appearing on the patient information sheet. Anonymity will be maintained throughout using non-identifiable index (codes) and data will be protected via encryption. Any images or videos stored will also be anonymised in the same way.

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

( ) Yes (●) No

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?

The patients will be approached by [NAME] or a clinical member of the research team, after their cases have been discussed at a multi-disciplinary cancer team meeting. Clinical members able to approach potential participants will include: -[NAME] and [NAME] who are both consultants within Imperial College Healthcare Trust whom the patients care will fall under -[NAME] who holds an honorary contract with the trust until 2022 -[NAME] (ECMC Research Nurse) who holds a licence to attend as a clinical trials practitioner until 2022 Strict inclusion and exclusion criteria will be adhered to. Patients will be approached at least two weeks before the surgery where a clinical member of the team will explain clearly the study, the risks or benefits associated with their participation and point out its voluntary nature. This will either happen during their initial outpatient surgical appointment where they discuss the operation, anaesthetic pre-assessment clinic, during the breast care nurse specialist meeting, or over the telephone. An invitation to partake in the study will be distributed alongside a patient information leaflet. Patients will have until the day of surgery to consider whether they want to participate. Patients who agree to participate will be asked to sign a consent form at the day of operation to document their agreement.

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.

Having received the patient information sheet 2 weeks in advance and discussed the details of the study with [NAME] or a member of the clinical team, patients will be asked to sign the consent form on the morning of their operation. At the same time, [NAME] or a member of the clinical team with knowledge of the protocol will re- explain and re-discuss the study with them with the help of the patient information sheet, answering any further questions they might have and ensuring them that they can change their mind at any time without any further effects on the standard of care they will receive.

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.Howlong will you allow potential participants to decide whether or not to take part?

They will be allowed to consider their involvement in the study from the time of the decision has been made for the patient to undergo the surgery up to the surgery itself (usually this is a few weeks). They will then be allowed questions and time to discuss with their relatives, family and friends. The patient information documents will be given out to them at least two weeks prior to their involvement, when they are first approached about the study. On the day of surgery, they will be approached about the study and the study will once again be explained to them in detail, using the information sheet. Patients of course, having given consent, will be allowed the opportunity to withdraw consent at any time prior to anaesthesia being administered, without the need for a reason.

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?
Patients will be asked during the consent process and the surgical team will make a decision on whether they should be included in this study based on their current commitment(s).

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)*

These patients will be given information on the study at the time of previously scheduled appointments and hence a translator, interpreter or sign language expert will already have been considered and be booked for this purpose, by the admitting clinical team and administration team. It is important that the patient is able to make an informed decision about participation in this study, and it will be sought to clearly identify this via the translator/interpreter, who will also be asked to counter-sign the consent form having ensured that the patient is in full agreement with participation and has no further questions. Should there be any doubts or concerns regarding understanding or inability to provide consent due to language barriers, the patient will not be recruited into the study.

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:

Patient will have to consent on the day of their surgery. If they lose the capacity to consent between the introduction of the study topic and the day of consent, then they will be excluded from the study.

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)*

- ☐ 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
- ☑ Use of audio/visual recording devices
- ☑ Storage of personal data on any of the following:
  - ☑ Manual files (includes paper or film)
  - ☐ NHS computers
  - ☐ Social Care Service computers
  - ☐ Home or other personal computers
  - ☐ University computers
  - ☐ Private company computers
  - ☑ Laptop computers

Further details:

The laptop interfacing with the cameras of the system during the acquisition, uses FileVault to encrypt its contents automatically (this would mean that it would require a login password to access the data. Should the password be forgotten, the data will be irretrievably lost). The images acquired during surgery and corresponding data will be immediately stored encrypted in a USB (SafeStick) Members of the research team at Imperial College London may also have access to the anonymized images made during surgery. Access to these images will only be available through the Department of Surgery and Cancer, Imperial College London. The named custodian is [NAME] / [NAME] will be formally responsible for the safe keeping, control of use and disposal of images (where no longer required) in accordance with the consent given by

the participants. They will be officially responsible to ensure that procedures and security arrangements are sufficient to prevent breaches of confidentiality. [NAME] / [NAME] will be responsible for keeping proper records of all uses that have been made of the material, whether by themselves or by others. Members of the research team that will view these anonymised images will not be able to identify individual research participants.

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

The encrypted USB (SafeStick) will be used to store the links between the patient data and the assigned study number/code. The laptop also uses FileVault to encrypt its contents automatically (this would mean that it would require a login password to access the data. Should the password be forgotten, the data will be irretrievably lost). Copies of Consent Forms, Patient Information Sheets or any other signed and name-labelled documentation will be archived in a password protected/ locked drawer. Chief Investigator, [NAME] will be responsible for the safekeeping of this information. They will be stored in a coded office, which is located in a code-accessed department.

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

The NHS Code of Confidentiality will be upheld. Patient's name will be anonymised into codes being the identifier of the personal data for that particular individual, and these will be encrypted. The custodian of the data and guardian of the codes, [NAME] / [NAME], will be formally responsible for the safekeeping, control of use and disposal of images (where no longer required) in accordance with the consent given by the participants. They will be officially responsible to ensure that procedures and security arrangements are sufficient to prevent breaches of confidentiality. [NAME] / [NAME will be responsible for keeping proper records of all uses that have been made of the material, whether by themselves or by others. Members of the research team that will view these anonymised images will not be able to identify individual research participants. Where linked anonymised images are provided to a third party, the custodian will ensure that the data contained will remain protected and anonymised.

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.*

Only direct care medical team and primary researchers will have access to the participants' personal data during the study. The Sponsor Representatives and the NHS Trust may audit the study and therefore access personal data. Consent will be obtained for this.

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 anonymized images and videos and all feedback will be assessed by [NAME] / [NAME], and members of their research teams.

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	Professor of [SUBJECT] in the Hamlyn Centre for Robotic Surgery, Institute of Global Health Innovation and Department of Surgery and Cancer at St. Mary's Hospital
Qualifications	MSci (1999) and PhD (2003) award in Physics (Imperial College London) Lectureship (2005) in the Institute of Biomedical Engineering
Work Address	Hamlyn Centre 415 Bessemer Building Exhibition Road
Post Code	SW7 2AZ
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:
It is College policy that all data relating to research be stored for 10 years (archived).

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

Years: 10
Months:

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

Research data (i.e. images) will be kept for 10 years after the clinical trial completion as this is the policy of Imperial College. Only the principal research collaborators will have access to the research data and reserve the permission to display them for presentation purposes. The password for the research data stored will not be shared. At all times patient anonymity and confidentiality will be actively pursued. When the data are to be erased, the encrypted USB (SafeStick) which will be used to store the links between the patient data and the assigned study number/code, will be physically destroyed. Record stating when, how and name of the study of which the data were destroyed will be kept.

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. 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.
The study is non interventional and does not meet the criteria for needing to register on a publicly accessible database

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

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

- ☑ Peer reviewed scientific journals
- ☑ Internal report
- ☑ Conference presentation
- ☐ Publication on website
- ☐ Other publication
- ☐ Submission to regulatory authorities
- ☐ Access to raw data and right to publish freely by all investigators in study or by Independent Steering Committee onbehalf 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?

Patient data will be coded and anonymised in the results section of data collection, and no names or hospital numbers will be used in conjunction with the data.

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.
Patients will be informed via summary letters of the results of the study to their homes. It will keep them in up-to-date with their involvement and if there is a significant publication derived from it, this will also be shared with the participants who wish to receive this information (indicated on their consent form).

5. Scientific and Statistical Review

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

- [x] Independent external review
- [ ] Review within a company
- [ ] Review within a multi−centre research group
- [x] 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, givedetails ofthe bodywhichhasundertakenthereview:
The study has been sanctioned by the Department of Surgery and Cancer at Imperial College London and The Hamlyn Centre for Robotic Surgery, Institute of Global Health Innovation. It has been approved by [NAME], Clinical Senior Lecturer in Breast Surgery and [NAME], Professor of Surgical Imaging.

The study will undergo peer review by experts external to Imperial College and its related hospitals. They will be selected and contacted through the Imperial Joint Research Compliance office.

The study's patient information sheet and informed consent has been iteratively developed with the feedback from a PPI group facilitated by [NAME] (Charing Cross Hospital). A PPI group meeting was held at Charing Cross hospital on [DATE], where the study was introduced by a research team member ([NAME] & [NAME]) with the help of explanatory handouts. The group advised on methodology, risk management and inclusion/exclusion criteria.

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
- [ ] 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
- [x] 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?

Primary Outcome measures for the study include:
1.Using fluorescence imaging data to classify and distinguish cancerous and normal tissue:
-quantitatively (based off tumour to noise background ratio)
-qualitatively (post-operative analysis by surgeons of images obtained and whether a difference between healthy and normal tissue was visible)
2. Sentinel node detection rate (#of patients with at least one SNL/ # total patients).

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

Secondary outcome measures include:
1) using the data obtained in this study to determine the power calculation for future studies.
2) Do the fluorophores used have any preference for cancer subtype?
3) Are the fluorophores used affected by the hormonal receptor status of the breast cancer (estrogen/ progesterone/ HER2)?

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:	80
Total international sample size (including UK):	0
Total in European Economic Area:	0

Further details:
This is an evaluation of fluorophores being used in a novel manner. We have chosen 40 patients per fluorophore in view of the heterogenous nature of breast cancer in order to assess whether there is predilection of the fluorophores for certain subtypes of cancers or receptor presence.

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.*

This group is large enough to allow for feasibility evaluation of the individual fluorophores. Given the heterogenous nature of breast cancer, we wanted a sufficient amount of patients to determine whether there was any predilection of the fluorophores for certain cancer types or hormonal expression. This is an early feasibility study which focuses on qualitative comparison of images with histological results.However, even at this early stage, it is essential to investigate the overall performance of the systems among common surgical scenarios and surgical procedures and thus the study is not limited to one case. 80 individual case scenarios are enough to fulfil this cause.

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.

The patients' data will be analysed qualitatively and quantitatively using image processing software, some of which will be written using common approaches such as Matlab, ImageJ etc. Each participant's images and videos will be reviewed off-line by surgeons to compare NIR fluorescence and multispectral images to white light images.

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	Professor of Surgical Imaging and Biophotonics
Qualifications	PhD
Employer	
Work Address	Hamlyn Centre 415 Bessemer Building Exhibition Road SW7
Post Code	2AZ
Telephone	[TELEPHONE]
Fax	[FAX]
Mobile	[MOBILE]
Work Email	[EMAIL]

Title Forename/Initials Surname

	[TITLE] [FORENAME] [SURNAME]
Post	Research Associate
Qualifications	PhD
Employer	Imperial College London
Work Address	Hamlyn Centre for Robotic Surgery Bessemer Building, South Kensington Campus Imperial College London
Post Code	SW7 2AZ
Telephone	[TELEPHONE]
Fax	[FAX]
Mobile	[MOBILE]
Work Email	[EMAIL]

Title Forename/Initials Surname

	[TITLE] [FORENAME] [SURNAME]
Post	Professor of Surgical Sciences
Qualifications	Mb BCh, FRCS, PhD, FRCS, MErgS, FRCS
Employer	Imperial College London
Work Address	Queen Elizabeth the Queen Mother Wing (QEQM) St Mary's Campus
Post Code	W2 2NY
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: Non-Commercial

If Other, please specify:

Contact person

Name of organisation	Imperial College
Given name Family name	[TITLE] [FORENAME] [SURNAME]
Address Town/city Post code	Room 221, Level 2, Medical school building, 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
- ☐ 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 NIHR
Address Room 132, Richmond House 79 Whitehall London

Post Code SW1A2NS
Telephone
Fax
Mobile
Email

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

Amount: 675756

Duration
Years: 3
Months:
If applicable, please specify the programme/ funding stream:
What is the funding stream/ programme for this research project?

Organisation Imperial College
Address Kensington
London

Post Code SW7 2AZ
Telephone [TELEPHONE]
Fax [FAX]
Mobile [MOBILE]
Email [EMAIL]

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

Date Funding decision expected: 01/07/2019

Amount: 60000

Duration
Years: 1
Months:
If applicable, please specify the programme/ funding stream:
What is the funding stream/ programme for this research project?
Imperial Confidence in Concept Grant

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	Imperial College
Address	Room 221, Level 2, Medical school building, Norfolk Place London
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:01/05/2019
Planned end date:01/06/2022
Total duration:
Years:3 Months:1 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)

LVLS

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 1

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:*

[x] NHS organisations in England	1
[ ] 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: 1

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 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 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.

☑ 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

Part B: Section 2

A. General information

Information in this sub-section will be included in applications to the Research Ethics Committee and NHS R & D offices at the research sites.

1. Is the manufacturer (or other organisation responsible for developing the device) the same organisation named as lead sponsor for this study?

(●) Yes ( ) No

Organisation	Imperial College
Address	Room 221, Level 2, Medical school building, Norfolk Place London
Post Code	W2 1PG
Country	
Telephone	[TELEPHONE]
Fax	[FAX]
Mobile	[MOBILE]
E-mail	[EMAIL]

2. Details of the medical devices to be used in the study

Name of the manufacturer:	Imperial College
Manufacturer's trade name for the device:	NIR fluorescence imaging
Device identification name and/or number:	
Name:	NA NA
Number:	NIR fluorescence imaging
Generic name of device and principal intended use(s):	
Length of time since device came into use:	1 year
Name of the manufacturer:	Imperial College London
Manufacturer's trade name for the device:	LCTF MSI
Device identification name and/or number:	
Name:	NA NA
Number:	LCTF MSI
Generic name of device and principal intended use(s):	
Length of time since device came into use:	2 years

3-1. Further details of the purpose of the study

Does the study involve:

- (●) Investigation of a new medical device
- ( ) Investigation of new implantable material
- ( ) Use of an existing product outside the terms of its CE market intended purpose
- ( ) Use of a modified product
- ( ) Use of an existing product within its CE market intended purpose

3-2. Please give further details below including the following:

Description of any new device, materials, method of use or operation with a summary of the intended purpose.

NIR fluorescence imaging uses near infrared light to illuminate the sample (non-contact) with a camera lens or endoscope used to collect infrared fluorescent light emitted. The light is filtered to select just the fluorescence on a sensitive camera. In white light mode, the tissue is illuminated and imaged onto an RGB camera. In different configurations, one or two cameras may be used in a composite camera head.
MSI imaging uses a tunable filter in front of a camera using non-contact imaging system such as a camera lens or endoscope depending on the setting. The filter is a liquid crystal tunable filter/electronically controllable filter wheel with different filters inserted within. Illumination is via non-contact white light delivered by standard light cable.

Composition of any new implantable materials, including summary of biocompatibility findings from studies to date.

NA

A summary of any modifications to CE marked devices.

NA

A summary of any proposed changes to the CE market intended purpose.

NA

For all products with CE mark please attach instructions for use.

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?

Human tissue which will be included in the study will be that which is obtained during the planned breast conserving surgery procedure. This will entail the tumour specimen, any potential cavity shave margins, as well as any lymph nodes which are excised during the procedure. No additional tissue will be collected than that which would have occurred during the planned breast conserving surgery.

2. Who will collect the samples?

The operating surgeon ([NAME] or [NAME]) will obtain the samples as per standard operating procedure during a breast conserving surgery +/- axillary procedure. These will then be passed on to the team to assess using the fluorescence guided imaging system, prior to being sent for formal histology as per hospital protocol.

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*

Inthis 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]*

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?

The tissue samples obtained during the breast conserving surgery will be immediately imaged using the Imperial camera fluorescence imaging system. After the images are taken, the samples will be sent for formal histology where they will be stored as per the histopathology department protocol. Some samples will also be sent for

immunohistochemistry staining at UCL in the case of EMI-137.

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.

Patients will have the option to hear about the results of the study should they be interested. However, the findings will have no clinical significance to them or their immediate relatives.

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

Samples obtained during the breast conserving surgery will be imaged using the fluorescence imaging system within the theatre. They will then be sent for formal histopathology as per hospital protocol where they will be stored accordingly. Images obtained during the surgery will be fully anonymized and stored on 2 USB Safesticks by the CI ([NAME]) and by the Academic Lead ([NAME]) for the research team to use.

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:

Samples obtained during the breast conserving surgery will be imaged using the fluorescence imaging system immediately within the theatre. The tissue will then be sent for formal histology as per hospital protocol where they will be stored accordingly in the pathology department.

The images obtained during the surgery will be fully anonymized and stored on 2 USB Safesticks by the CI ([NAME]) and by the Academic Lead ([NAME]) for the research team to use. This will then be stored for 10 years as per Imperial College Research Protocol.

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	[FORENAME] [SURNAME] [EMAIL]
	Organisation name	IMPERIAL COLLEGE HEALTHCARE NHS TRUST	Qualification (MD...)	QUALIFICATIONS]
	Address	ST. MARYS HOSPITAL PRAED STREET LONDON GREATER LONDON	Country	UNITED KINGDOM
	Post Code	W2 1NY		
	Country	ENGLAND		

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 fulfil the responsibilities of the chief investigator for this study as set out in the UK Policy Framework for Health and Social Care Research.

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

4. 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.

5. 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.

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

7. 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.

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

9. 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 2018.

10. 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.

11. 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 2018.

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 Health Research Authority (HRA) together with the contact point for enquiries named below. Publication will take place no earlier than 3 months after the issue of the ethics committee's final opinion or the withdrawal of the application.

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

HRA 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 [NAME] on 03/07/2019 14:09.

Job Title/Post:

Organisation:

Email:

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 responsibilities of sponsors set out in the UK Policy Framework for Health and Social Care Research will be fulfilled in relation to this research.

   Pleasenote: *The declarations below do not formpart of the application for approval above. They will not be considered by the Research Ethics Committee.*

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

8. 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 Ruth Nicholson on 03/07/2019 11:58.

Job Title/Post:	Head of Research Governance and Integrity
Organisation:	Imperial College London
Email:	r.nicholson@imperial.ac.uk

D3.Declaration for student projects by academic supervisor(s)

1.Ihave read and approved both the research proposal and this application. I am satisfied that the scientific content ofthe research is satisfactory for an educational qualification at this level.

2. I undertake to fulfil the responsibilities of the supervisor for this study as set out in the UK Policy Framework for Health and Social Care Research.

3. I take responsibility for ensuring that this study is conducted in accordance with the ethical principles underlying the Declaration of Helsinki and good practice guidelines on the proper conduct of research, in conjunction with clinical supervisors as appropriate.

4. I take responsibility for ensuring that the applicant is up to date and complies with the requirements of the law and relevant guidelines relating to security and confidentiality of patient and other personal data, in conjunction with clinical supervisors as appropriate.

Academic supervisor 1

This section was signedelectronically by Dr Daniel Elson on 03/07/2019 14:41.

Job Title/Post:	Professor of Surgical Imaging
Organisation:	Imperial College London
Email:	ds.elson@imperial.ac.uk