

# A study to investigate HPV-detect, a new way to measure the response to treatment in patients with Human Papilloma Virus (HPV) positive head and neck cancer

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<b>Registration date</b> 03/03/2020	<b>Overall study status</b> Completed	<input type="checkbox"/> Statistical analysis plan <input type="checkbox"/> Results
<b>Last Edited</b> 21/10/2025	<b>Condition category</b> Cancer	<input type="checkbox"/> Individual participant data <input checked="" type="checkbox"/> Record updated in last year

## Plain English summary of protocol

### Background and study aims

Following curative chemo-radiation (CRT), about 20-30% of patients with locally advanced human papillomavirus related (positive) oropharyngeal cancer (HPV+OPC) undergo unnecessary neck dissection or biopsies based on positive or equivocal post-CRT 18F-FDG PET-CT (PET-CT). As the positive predictive value of such PET scans is sub-optimal, a more reliable marker of 'true' residual disease is required as a means of guiding management decisions. The newly developed ultra-sensitive and specific assay 'HPV-detect' can non-invasively measure the post-CRT plasma HPV DNA levels, and can be used to guide management decisions potentially avoiding unnecessary surgical procedures. The aim of this study is to find out whether HPV DNA measured using HPV-detect is a predictor of the absence of residual disease following primary RT/CRT for HPV+ positive oropharyngeal cancer.

### Who can participate?

Patients aged 18 or over with squamous cell carcinoma of the oropharynx undergoing curative RT/CRT

### What does the study involve?

This is a sample and data collection/analysis study only. Diagnostic tumour biopsy blocks are required for all patients. Blood samples will be collected from consenting HPV+ patients at baseline, weekly during CRT, weekly for 4 weeks after treatment, at 6 weeks, 3, 6, 9 and 12 months after CRT. HPV negative patients will donate samples at baseline, at 6 weeks, and at 3, 6, 9 and 12 months only. In HPV+ patients an additional tissue sample will also be collected after any surgical procedures and/or biopsies and additional blood samples will also be obtained before and after any surgical procedure or biopsy.

### What are the possible benefits and risks of participating?

There is no direct benefit for individual patients participating in this study. It is hoped that the information gained from this study will help to improve the treatment options and/or quality of

life for patients with HPV-positive locally advanced head and neck cancer in the future. Patients will be asked to donate blood samples during the study, which may be associated with some degree of discomfort, risk of bleeding or infection. However, it is anticipated that the risks associated with these procedures will be minimal. Blood samples collected up to the 3-month timepoint will be taken at the same time as routine blood samples. Blood sampling at the routine follow up appointment after 3 months may be in addition to standard practice at some centres. Tissue blocks will be requested from tissue taken routinely at diagnosis and after any surgery or biopsies performed post (chemo)radiotherapy.

Where is the study run from?

Cancer Trials and Statistics Unit, Institute of Cancer Research (UK)

When is the study starting and how long is it expected to run for?

May 2019 to September 2025

Who is funding the study?

Medical Research Council (UK)

Who is the main contact?

Dr Marie Emson

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## Contact information

### Type(s)

Scientific

### Contact name

Dr Marie Emson

### Contact details

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## Additional identifiers

### Clinical Trials Information System (CTIS)

Nil known

### Integrated Research Application System (IRAS)

237168

### ClinicalTrials.gov (NCT)

Nil known

**Protocol serial number**

CPMS 42229, IRAS 237168

## Study information

**Scientific Title**

Investigation of novel plasma Human Papilloma Virus DNA assay for treatment response estimation in head and neck cancer

**Acronym**

INOVATE

**Study objectives**

Approximately 2000 patients are diagnosed annually in the UK with oropharyngeal (throat) cancer caused by human papillomavirus (HPV) infection. The standard treatment is chemotherapy and radiotherapy followed by surgical removal of any cancer left behind. The surgery is undertaken based on results of a scan (18F-FDG PET-CT). However, approximately 20-30% of patients will receive unnecessary surgical intervention, as residual cancer is not confirmed on pathological examination post-surgery. Following surgery approximately 25% of patients will have immediate complications and all will suffer significant permanent side effects (pain, shoulder dysfunction, altered quality of life). Therefore a more reliable marker of true residual disease is required as a means of guiding management decisions.

As HPV positive(+) oropharyngeal cancers release HPV-DNA into the blood stream its presence can serve as a detection marker of residual cancer after treatment. HPV-detect, an assay developed and tested in a single-centre, prospective pilot study at the Royal Marsden Hospital /Institute of Cancer Research, is a way to measure HPV-DNA levels using a blood test. Further validation of HPV-detect is now required in a prospective multi-centre study. The study is needed to establish its usefulness in patient care and evaluate its potential to predict the absence of residual disease and avoid unnecessary surgery. INOVATE is a multicentre study which aims to collect biological samples from 143 HPV+ and 48 HPV negative patients with oropharyngeal cancer. Patients will be asked to donate archival diagnostic tumour tissue samples and blood samples taken at specified time points up to 1 year following treatment. HPV-DNA levels will be measured using HPV-detect and the results correlated with the 18F-FDG PET-CT results at 12 weeks. In addition, barriers to adoption of the test and how to address these will be studied. A health economic analysis will study the cost benefits of implementing the test in the UK.

**Ethics approval required**

Old ethics approval format

**Ethics approval(s)**

Approved 30/10/2019, London - Bloomsbury Research Ethics Committee (HRA RES Centre Manchester, Barlow House 3rd Floor, 4 Minshull Street, Manchester, M1 3DZ, UK; Tel: +44 (0)207 104 8127; Email: nrescommittee.london-bloomsbury@nhs.net)ref: 19/LO/1558

**Study design**

Non-randomized observational cross-sectional

**Primary study design**

Observational

## **Study type(s)**

Diagnostic

## **Health condition(s) or problem(s) studied**

Head and neck cancer

## **Interventions**

INOVATE is a multicentre prospective biological sample collection and analysis study which aims to validate circulating Human Papilloma Virus (HPV) DNA as a marker of residual disease in patients with HPV+ oropharyngeal cancer. The study will be open to newly diagnosed patients with HPV+ and HPV- tumours (negative controls) who are due to receive radical radiotherapy alone or chemotherapy and radiotherapy (RT/CRT). The study will comprise the collection and analysis of tissue and blood samples. For tissue samples, the researchers will request and use the archival formalin-fixed paraffin-embedded blocks from biopsies obtained for the diagnosis of cancer or at surgery. Therefore, no additional biopsies will be required. Venous blood samples will be collected before treatment and at regular intervals during and following completion of treatment.

Patient suitability for the study will initially be assessed at the multidisciplinary team's (MDT) assessment meeting. Any patient who expresses an interest and is technically suitable for the study will be informed about the INOVATE study.

Following the discussion patients will be given the patient information sheet. It is proposed that as this is not a treatment study any patient who requests to consent to the study on the same day will be allowed to do so. Patients who wish to consider their participation in the study will be invited to return to the hospital at least 24 hours later to confirm participation and to sign the consent form.

## **SCREENING ASSESSMENTS**

There are no additional screening assessments specific to the INOVATE study. It is anticipated that patients will be screened prior to standard treatment with RT/CRT as per local practice. Consenting patients will be registered into the study after diagnosis, routine screening and confirmation of HPV status. All patients will be required to donate a blood sample at baseline ie after registration but before any standard treatment commences.

HPV negative patients will be requested to donate further blood samples at 6 weeks post-RT /CRT and at 3, 6, 9 and 12 months after treatment.

HPV positive patients will be requested to donate blood samples weekly during RT/CRT and weekly for 4 weeks thereafter, at 6 weeks, 3, 6, 9 and 12 months post-CRT. If the patient's RT treatment is extended into week 7 an additional blood sample will be taken to ensure that a sample is collected at the end of treatment. Additional tissue and blood samples will also be requested for HPV+ patients before and after any surgical procedures or biopsies performed post-RT/CCRT. Tissue collected at this time is part of the centres' routine practice and the study will request access to these tissue blocks.

Blood samples collected up to the 3-month timepoint will be taken at the same time as routine blood samples. Blood sample donation at the routine follow up appointment post-3 months may be in addition to standard practice at some centres. Centres are advised to inform patients that some samples may be in addition to standard practice during the informed consent process and this is also detailed in the patient information sheet.

## **FOLLOW UP**

There are no scheduled follow up visits for INOVATE. However, data will be collected from the patients' routine follow up visits following treatment according to local practice.

Approx 12 weeks after the completion of RT/CRT all patients will be routinely required to have an 18F-FDG-PET-CT scan to assess response to treatment. All centres who have expressed an interest in taking part in INOVATE have confirmed that this scan is used routinely at 12 weeks at their centres. ICR-CTSU will collect data from 18F-FDG PET-CT scans performed as part of routine practice. Sites are requested to send a copy of the report for the 3 month 18F-FDG PET-CT scan to the ICR-CTSU office. This report should be redacted to protect the patient's personal data.

ICR-CTSU may request redacted reports of other 18F-FDG PET-CT scans carried out during the lifetime of the study.

It is anticipated that patients with equivocal PET-CT and a lymph node greater than 1cm or a positive PET-CT will be routinely recommended to have a biopsy and/or neck dissection. The type of surgery will be at the discretion of the local MDT.

Clinical data will be collected by ICR-CTSU from routine follow up appointments until 12 months post-RT/CCRT but this will not require any additional visits or action from the participants in the study. Sites will be requested to report any confirmation of residual disease at 12 weeks or later confirmation of disease progression/recurrence to the ICR-CTSU Trials Office on eCRFs. If HPV+ patients are required to progress to surgery/biopsies sites are asked to notify ICR-CTSU in an expedited manner on the appropriate eCRF. This will enable ICR-CTSU to prompt sites about the additional tissue and blood sample collection for HPV+ patients who will be scheduled for surgery.

#### **STAKEHOLDER ANALYSIS AND HEALTH ECONOMICS STUDY**

The National Institute for Health Research London in vitro Diagnostics Cooperative (NIHR London IVD) at Imperial will undertake stakeholder analyses to understand risks, adoption barriers and assess the potential impact of HPV-detect in the NHS. This study will involve members of the research team at participating sites who may be selected to be interviewed on a one-to-one basis about current use of HPV-detect and to identify user needs, user experience, perceived trust and acceptance of the use of HPV-detect.

PLEASE NOTE: The details of the health economics study will be added to the protocol by amendment prior to initiation.

The patient information sheet (PIS) will inform the patient about the clinical data collection for the study. The PIS will also clearly state that patients, their research doctors and other members of the patient's clinical care team at the site will not be informed of their HPV-detect test result and that the result will not affect their future treatment.

#### **Intervention Type**

Other

#### **Primary outcome(s)**

The specificity of HPV-detect (using plasma HPV DNA levels) in correctly identifying those with no residual disease, at 3 months following completion of primary RT/CRT; defined as the proportion of patients who are HPV-detect negative among those with no residual disease according to 18F-FDG PET at the same timepoint.

#### **Key secondary outcome(s)**

1. The sensitivity of HPV-detect (using plasma HPV DNA levels) in correctly identifying those with residual disease at 3 months following completion of primary RT/CRT; defined as the proportion of patients who are HPV-detect positive among those with residual disease according to 18F-FDG PET-CT at the same timepoint
2. The proportion of patients who have no residual disease on biopsy/neck dissection amongst

those with residual disease according to 18F FDG PET-CT but HPV-detect negative at 3 months after primary RT/CRT

3. Repeated measures of plasma HPV DNA levels up to a period of 12 months post RT/CRT (timepoints defined in the Interventions field) will be associated with the clinical and radiological response

4. Sensitivity and specificity of HPV-detect in measuring plasma HPV DNA levels compared with HPV DNA levels from diagnostic tissue at baseline; defined as the proportions of true positives and the proportions of true negatives, respectively

5. The pattern of plasma HPV DNA responses to RT/CRT presented by calculating the percentage change in HPV DNA level at each assessment timepoints from baseline (timepoints defined in the Interventions field)

### **Completion date**

15/09/2025

## **Eligibility**

### **Key inclusion criteria**

1. Aged 18 years or above.
2. Newly diagnosed patients with T1-T2/N1-3 or T3-T4/ N0-3 squamous cell carcinoma of the oropharynx
3. Availability of tissue from one archival diagnostic tumour tissue block
4. Confirmed HPV status (p16InK4A IHC/ISH)
5. Patients must be candidates for and willing to undergo curative RT/CRT
6. Written informed consent

### **Participant type(s)**

Patient

### **Healthy volunteers allowed**

No

### **Age group**

Adult

### **Lower age limit**

18 years

### **Sex**

All

### **Total final enrolment**

191

### **Key exclusion criteria**

1. Previous or concurrent illness or situation, which in the investigator's opinion would interfere with collection of the complete sample collection
2. Any invasive malignancy within previous 5 years (other than non melanomatous skin carcinoma or cervical carcinoma in situ)
3. Clinical evidence of metastatic disease

**Date of first enrolment**

10/01/2020

**Date of final enrolment**

11/05/2022

**Locations****Countries of recruitment**

United Kingdom

England

Northern Ireland

Scotland

Wales

**Study participating centre**

**The Royal Marsden NHS Foundation Trust**

Fulham Road

London

United Kingdom

SW3 6JJ

**Study participating centre**

**Royal United Hospitals Bath NHS Foundation Trust**

Combe Park

Bath

United Kingdom

BA1 3NG

**Study participating centre**

**James Cook University Hospital**

South Tees Hospitals NHS Foundation Trust

Marlon Road

Middlesbrough

United Kingdom

TS4 3BW

**Study participating centre**

**Royal Hallamshire Hospital**

Glossop Road  
Sheffield  
United Kingdom  
S10 2JF

**Study participating centre****Southampton General Hospital**

University Hospital Southampton NHS Foundation Trust  
Tremona Road  
Southampton  
United Kingdom  
SO16 6YD

**Study participating centre****Norfolk and Norwich University Hospitals NHS Foundation Trust**

Colney Lane  
Colney  
Norwich  
United Kingdom  
NR4 7UY

**Study participating centre****University Hospital Aintree**

Aintree University Hospital NHS Foundation Trust  
Fazakerley Hospital  
Lower Lane  
Liverpool  
United Kingdom  
L9 7AL

**Study participating centre****Queens Medical Centre**

Nottingham University Hospitals NHS Trust  
Trust Headquarters  
Derby Road  
Nottingham  
United Kingdom  
NG7 2UH

**Study participating centre**

**Colchester District General Hospital**

East Suffolk And North Essex NHS Foundation Trust  
Turner Road  
Colchester  
United Kingdom  
CO4 5JL

**Study participating centre**

**University Hospitals Bristol NHS Foundation Trust**

Marlborough Street  
Bristol  
United Kingdom  
BS1 3NU

**Study participating centre**

**Queen Alexandra Hospital**

Portsmouth Hospitals NHS Trust  
Southwick Hill Road  
Portsmouth  
United Kingdom  
PO6 3LY

**Study participating centre**

**Beatson West of Scotland Cancer Centre**

1053 Great Western Road  
Glasgow  
United Kingdom  
G12 0YN

**Study participating centre**

**Clatterbridge Cancer Centre**

Clatterbridge Hospital  
Clatterbridge Road  
Wirral  
United Kingdom  
CH63 4JY

**Study participating centre**

**Velindre Hospital**

Velindre Road  
Cardiff

United Kingdom  
CF14 2TL

## Sponsor information

### Organisation

The Institute of Cancer Research, London

### ROR

<https://ror.org/00xmdg797>

## Funder(s)

### Funder type

Research council

### Funder Name

Medical Research Council; Grant Codes: MR/R015589/1

### Alternative Name(s)

Medical Research Council (United Kingdom), UK Medical Research Council, Medical Research Committee and Advisory Council, MRC

### Funding Body Type

Government organisation

### Funding Body Subtype

National government

### Location

United Kingdom

## Results and Publications

### Individual participant data (IPD) sharing plan

The datasets generated during and/or analysed during the current study are/will be available upon request from [inovate-icrctsu@icr.ac.uk](mailto:inovate-icrctsu@icr.ac.uk).

### IPD sharing plan summary

Available on request

### Study outputs

<b>Output type</b>	<b>Details</b>	<b>Date created</b>	<b>Date added</b>	<b>Peer reviewed?</b>	<b>Patient-facing?</b>
<a href="#">HRA research summary</a>			28/06/2023	No	No
<a href="#">Protocol file</a>	version 2.0	27/09/2021	19/05/2022	No	No
<a href="#">Study website</a>	Study website	11/11/2025	11/11/2025	No	Yes