
# Accelerated Hypofractionation, Chemotherapy, Intensity Modulation and Evaluation of Dose Escalation in Oropharyngeal Cancer

## Protocol Version 4.0, 10 September 2013

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|---|---|
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## SIGNATURE PAGE

ArChIMEDEs-Op, Protocol Version 4.0, 10 September 2013

**This protocol has been approved by:**

**Name:** Dr. Paul Sanghera **Study Role:** Chief Investigator

**Signature:** _____ **Date:** DD / MON / YYYY

This protocol describes the ArChIMEDEs-Op study and provides information about procedures for patients taking part in the ArChIMEDEs-Op study. The protocol should not be used as a guide for treatment of patients not taking part in the ArChIMEDEs-Op study.

## AMENDMENTS

The following amendments and/or administrative changes have been made to this protocol since the implementation of the first approved version

| Amendment number | Date of amendment | Protocol version number | Type of amendment | Summary of amendment |
|---|---|---|---|---|
| 1 | 1 June 2012 | 2.0 | Substantial amendment | Clarification of withdrawal arrangements and change in tissue sample storage |
| 2 | 5 December 2012 | 3.0 | Substantial amendment | Change in eligibility criteria and contra-indicative treatment |
| 3 | 10 September 2013 | 4.0 | Substantial amendment | Clarification of eligibility criteria; induction chemotherapy permitted as per local policy and addition of separate concurrent and induction chemotherapy treatment forms to CRF table; clarification of SAE reporting |

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## STUDY SYNOPSIS

### TITLE

**A**ccelerated Hypofractionation, **C**hemotherapy, **I**ntensity **M**odulation and **E**valuation of **D**ose **E**scalation in **O**ro**p**haryngeal Cancer (ArChIMEDEs-Op)

### TRIAL DESIGN

Single-centre, single-arm, feasibility study

### OBJECTIVE

To determine whether it is safe and feasible to deliver a 5 week schedule of dose escalated intensity modulated chemoradiotherapy for poor prognosis patients with locally advanced squamous carcinoma of the oropharynx (SCCOP) in the context of a feasibility study

### OUTCOME MEASURES

**Primary:**

- Full radiotherapy has been received as planned and the absence of consequential damage: defined by the absence of Grade 3 mucositis at 3 months

**Secondary:**

- Duration of Grade 3 mucositis: defined as the number of days of Grade 3 mucositis according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 3
- Incidence of acute Grade 4 toxicity defined according to the NCI CTCAE version 4
- Incidence of ≥ Grade 3 late toxicity defined according to the Radiation Therapy Oncology Group (RTOG) and NCI CTCAE version 4 scoring systems
- Complete response rate at 3 months defined as no clinically visible (including endoscopic evaluation), palpable or measurable disease on imaging OR the absence of residual tumour on directed biopsy/neck dissection. The primary tumour and regional lymph nodes will be considered separately
- 2 year local control defined as no re-appearance of tumour within primary site (including immediately adjoining anatomical sites) or regional lymph nodes after complete response
- 2 year disease free survival defined in whole days, as the time from entry into the study until disease recurrence or death from any cause, whichever is first. Patients will be censored at the date last seen alive and relapse free. All patients will be followed up for at least 5-years
- 2 year overall survival defined in whole days as the time from entry into the study until death from any cause. Patients will be censored at the date last seen alive. All patients will be followed up for at least 5-years
- Incidence of feeding tube dependency at one year defined by the patient requiring supplementation of nutrition by a feeding tube

## PATIENT POPULATION

Patients with HPV and P16 negative locally advanced squamous carcinoma of the oropharynx or patients with P16 positive tumours if stage N2b-3 and greater than 10 pack year history of smoking

## SAMPLE SIZE

15 patients

## INCLUSION CRITERIA

1. Histologically proven, P16 negative SCCOP deemed suitable for radical primary chemoradiotherapy with curative intent requiring bilateral neck irradiation or patients with P16 positive tumours if stage N2b-3 and greater than 10 pack year history of smoking. Neoadjuvant chemotherapy and pre or post chemoradiation neck dissections are permitted
2. Only patients requiring bilateral radiotherapy
3. Age ≥18 and <75 years
4. World Health Organisation (WHO) performance status 0 or 1
5. Adequate bone marrow: absolute neutrophil count > 1,800 cells/$mm^3$, platelets > 100,000 cells/$mm^3$, haemoglobin > 8.0 g/dl
6. Creatinine clearance > 50 ml/minute
7. Informed consent

Clinical and pathological staging is performed according to the International Union Against Cancer, Classification of Malignant Tumours Staging Manual (UICC TNM) -6th edition (Sobin, 2002).

## EXCLUSION CRITERIA

1. Prior invasive malignancy (except basal cell carcinoma and cervical intraepithelial neoplasia) within last 3 years
2. Prior radiotherapy to the head and neck region
3. Pregnancy and/or lactation
4. Reproductive capability and dis-agreement to use contraceptive
5. Contraindications to cisplatin and carboplatin chemotherapy including active vascular disease (e.g. myocardial within last 6 months, angina and symptomatic peripheral vascular disease)
6. Non curative intent
7. Non squamous cell carcinoma histology
8. Nasophaynx, larynx, hypopharynx, salivary gland or sino-nasal primary site
9. Other physical or psychiatric disorder that may interfere with subject compliance, adequate informed consent, follow up or determine the causality of adverse events
10. Suitable for unilateral radiotherapy

## TRIAL DURATION

24 months

## STUDY OFFICE CONTACT DETAILS

### Enquires:

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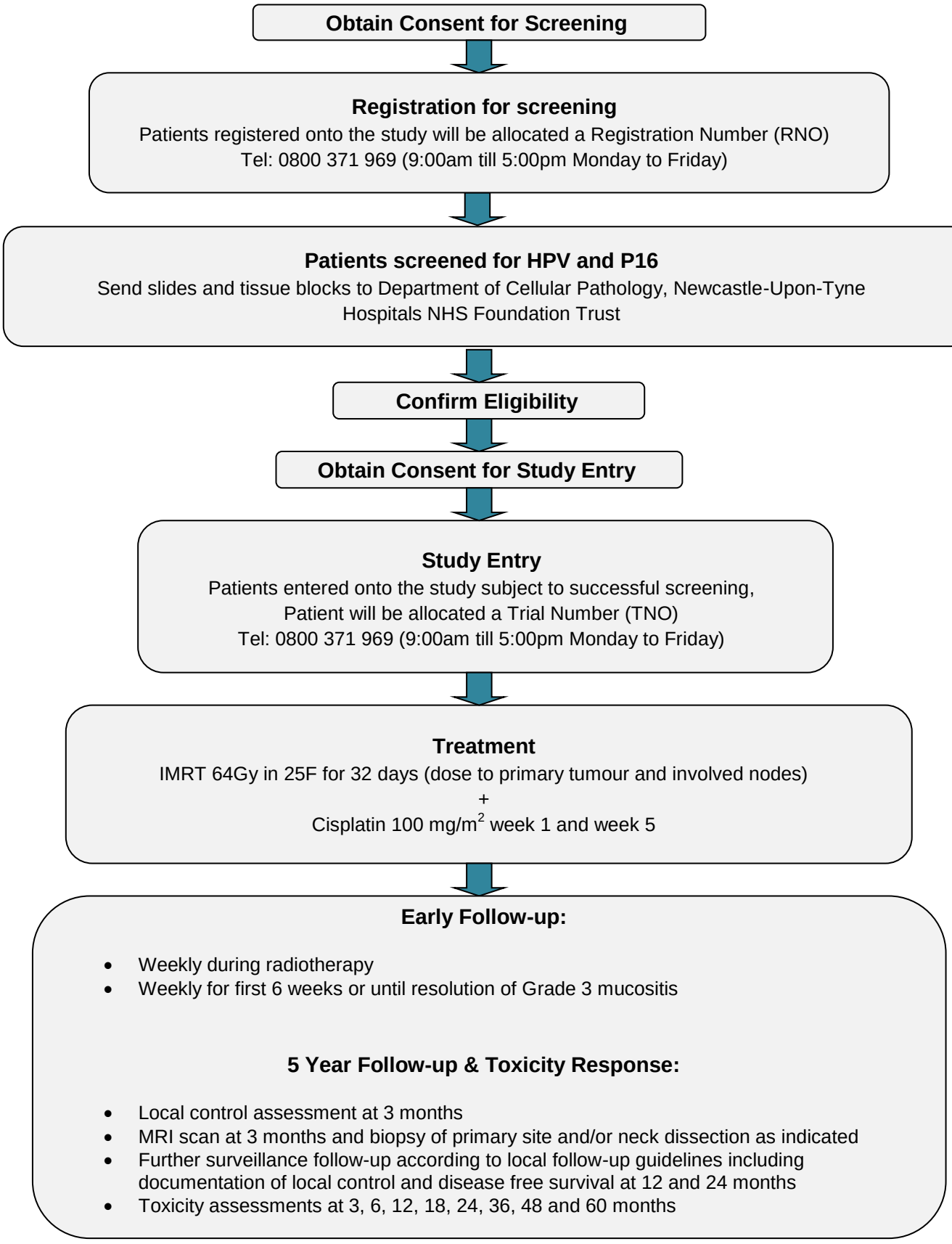
### Registration of Patients:

**Tel: 0800 371 969 (9:00am till 5:00pm Monday to Friday)**

### Serious Adverse Event Reporting:

**Fax: 0121 414 8392**

## STUDY SCHEMA



## SCHEDULE OF EVENTS

### SCREENING

Patients will be recruited if they have locally advanced SCCOP, confirmed on biopsy. Patients with HPV and P16 negative locally advanced squamous carcinoma of the oropharynx or patients with P16 positive tumours if stage N2b-3 and greater than 10 pack year history of smoking will be eligible. Only patients requiring bilateral neck radiotherapy will be suitable. These patients will be invited to participate in the study.

### BASELINE

- Physical examination including endoscopic examination of the primary site with biopsy. In most cases this will require examination under general anaesthetic
- Weight and WHO performance status
- Urea, creatinine, sodium, potassium, magnesium
- Glomerular Filtration Rate (GFR)
- Haemoglobin (Hb), white blood cell (WBC) and platelet counts
- Liver Function Tests (LFTs)
- Computed Tomography (CT) scan and Magnetic Resonance Imaging (MRI) scan of primary site and neck
- CT scan chest
- Dietary assessment (including assessment for percutaneous feeding tube)
- Dental assessment

### STUDY TREATMENT

- Intensity Modulated Radiotherapy (IMRT) 64Gy/25F to the primary tumour and involved nodes with elective irradiation of clinically uninvolved nodes to a dose of 50Gy/25F. An intermediate dose of 56Gy/25F will be delivered to regions deemed at high risk of microscopic disease (this will include anatomical regions at high risk of disease) according to the contouring protocol as stated in section 6.1.5.
- Treatment period
    - 1 treatment a day for 32 days (5 weeks) excluding Saturdays and Sundays
- Treatment should be completed within 32 days which will require compensation for any breaks in treatment due to logistics (for example, machine breakdown)
- Chemotherapy (Cisplatin) given as standard care:
    - Dose: Cisplatin 100 mg/m$^2$
    - Dosing schedule: Cisplatin 100 mg/m$^2$ will be administered on day 1 of week 1 and day 1 of week 5
    - Route/mode of administration: intravenous as a day case

If Cisplatin is contraindicated (e.g. renal impairment), Carboplatin AUC 5 week 1 and week 5 will be used consistent with standard care.

## RADIOTHERAPY

IMRT using static or rotational techniques will be performed according to institutional policy using existing software.

There will be strict adherence to the radiotherapy contouring protocol with a contouring review exercise prior to commencement according to the contouring protocol as stated in section 6.1.5.

To reduce toxicity, there will only be a 5-10 mm margin on the gross tumour volume to produce a clinical target volume (CTV64). The intermediate dose level will be used to treat tissue beyond this margin considered to be at risk of microscopic disease. Planning target volume margins beyond this will be according to institutional data.

## ON TREATMENT ASSESSMENTS

Clinical evaluation will be performed weekly during radiotherapy or until resolution of Grade 3 mucositis according to the NCI CTCAE version 3. The NCI CTCAE version 4.0 toxicity scale will be used to grade acute side effects. Full blood count, urea, electrolytes and creatinine will be performed weekly during radiotherapy. Dietary assessment will also be performed weekly.

## DOSE MODIFICATION AND RADIOTHERAPY TREATMENT BREAKS

Treatment breaks are only allowed for medical reasons and not social or logistical reasons. Any radiotherapy treatment break due to toxicity should be recorded in the patient's medical notes with documentation of reasons.

## 5 YEAR FOLLOW-UP

All patients, provided that they have not withdrawn consent to follow-up, should have long-term follow-up of at least 5 years, irrespective of whether they discontinued study treatment prematurely. The anticipated frequency is:

### Early Post Radiotherapy Follow-up:

- Weekly follow-up and documentation of acute toxicity for a minimum of 6 weeks post radiotherapy *or* until resolution of Grade 3 mucositis

### Late Follow-up and Response Assessment:

- Local control documentation at 3 months determined by clinical evaluation (including nasoendoscopy) and MRI scan of head and neck. Directed biopsy should be performed in patients with suspicion of local residual disease. A neck dissection is required for patients with persistent neck disease (clinical or radiological suspicion). Post chemoradiotherapy neck dissection may also be carried out on patients who originally presented with N2/N3 disease as a planned procedure.
- Thereafter, follow-up according to established local protocols (for example, monthly for the 1$^{st}$ year and every 8 weeks for the 2$^{nd}$ year)
- Documentation of local control and disease free survival is required at 12 and 24 months
- Late toxicity assessment will be recorded at 3, 6, 12, 18, 24 36, 48 and 60 months using NCI CTCAE version 4 and RTOG scoring systems

## SCHEDULE OF EVENTS FLOWCHART

| Assessment | Screening | Pre-study Entry | Pre-radiotherapy | During Radiotherapy (week) | | | | | Early Post Treatment (week) | | | | | | | Long term follow up (month) | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 3 | 6 | 12 | 18 | 24 | 36 | 48 | 60 |
| Obtain consent | x | x | | | | | | | | | | | | | | | | | | | | | |
| Confirm Eligibility (including CXR;FBC;CrCl) | x | x | | | | | | | | | | | | | | | | | | | | | |
| Histology report including p16 and HPV | | x | | | | | | | | | | | | | | | | | | | | | |
| Staging CT/MRI H&N | | x | | | | | | | | | | | | | | | | | | | | | |
| Dental assessment | | | x | | | | | | | | | | | | | | | | | | | | |
| Nutrition assessment | | | x | x | x | x | x | x | | | | | | | | | | | | | | | |
| Plan evaluation | | | x | | | | | | | | | | | | | | | | | | | | |
| Baseline toxicity | | | x | | | | | | | | | | | | | | | | | | | | |
| Acute toxicity | | | | | x | x | x | x | x | x | x | x | x | x | x | | | | | | | | |
| Chemotherapy and Radiotherapy compliance | | | | | | | | | x | | | | | | | | | | | | | | |
| Late toxicity | | | | | | | | | | | | | | | | x | x | x | x | x | x | x | x |
| Disease response | | | | | | | | | | | | | | | | x | x | x | x | x | x | x | x |

## ABBREVIATIONS

| | |
|---|---|
| **a/b** | Alpha/beta |
| **AE** | Adverse Event |
| **BD** | Twice Daily |
| **BED** | Biological Effective Dose |
| **CPA** | Clinical Pathology Accreditation |
| **CR** | Complete Response |
| **CRCTU** | Cancer Research Clinical Trials Unit |
| **CRF** | Case Report Form |
| **CT** | Computed Tomography |
| **CTV** | Clinical Target Volume |
| **CV** | Curriculum Vitae |
| **DAHANCA** | Danish Head and Neck Cancer Group |
| **DFS** | Disease Free Survival |
| **DMC** | Data Monitoring Committee |
| **DNA** | Deoxyribonucleic acid |
| **DSUR** | Development Safety Update Report |
| **DVH** | Dose Volume Histograms |
| **EORTC QLQ C30** | European Organisation for Research and Treatment of Cancer Quality of Life Questionnaires |
| **F** | Number of fractions |
| **FBC** | Full Blood Count |
| **GP** | General Practitioner |
| **GCP** | Good Clinical Practice |
| **GFR** | Glomerular Filtration Rates |
| **GTV** | Gross Tumour Volume |
| **GTVp** | Primary Gross Tumour Volume |
| **GTVn** | Nodal Gross Tumour Volume |
| **Gy** | Gray |
| **Hb** | Haemoglobin |
| **H&E** | Haematoxylin & Eosin |
| **HPV** | Human Papillomavirus |
| **HBRC** | Human Biomaterial Resource Centre |
| **ICF** | Informed Consent Form |
| **ICH GCP** | International Conference on Harmonisation Guidelines for Good Clinical Practice |
| **IHC** | Immunohistochemistry |
| **IMP** | Investigational Medicinal Product |
| **IMRT** | Intensity Modulated Radiotherapy |
| **IRB/IEC** | Institutional Review Board/Independent Ethics Committee |
| **ISF** | Investigator Site File |
| **ISH** | *In situ* hybridisation |
| **IV** | Intravenous |
| **kVCT** | kilo voltage computerised tomography |
| **LC** | Local Control |
| **LFTs** | Liver Function Tests |
| **MHRA** | Medicines for Healthcare products Regulatory Agency |
| **MDT** | Multidisciplinary Team |

| | |
|---|---|
| **MRI** | Magnetic Resonance Imaging |
| **MVCT** | Daily images |
| **NCI CTCAE** | National Cancer Institute Common Terminology Criteria for Adverse Events |
| **NHS** | National Health Service |
| **NG** | Nasogastric |
| **NOS** | Not otherwise specified |
| **NRES** | National Research Ethics Service |
| **OAR** | Organ-At-Risk |
| **OPC** | Oropharyngeal Cancers |
| **OPSCC** | Oropharyngeal squamous cell carcinoma |
| **OS** | Overall Survival |
| **PD** | Progressive Disease |
| **PEG** | Percutaneous Endoscopic Gastrostomy |
| **PET-CT** | Positron Emission Tomography – Computed Tomography |
| **PIS** | Patient Information Sheet |
| **PR** | Partial Response |
| **PRV** | Planning organ at Risk Volume |
| **PTV** | Planning Target Volume |
| **QA** | Quality Assurance |
| **QDS** | Four times daily |
| **QoL** | Quality of Life |
| **RCR** | Royal College of Radiologists |
| **R&D** | Research and Development |
| **REC** | Research Ethics Committee |
| **RECIST** | Response Evaluation Criteria In Solid Tumours |
| **RT** | Radiotherapy |
| **RTOG** | Radiation Therapy Oncology Group |
| **SAE** | Serious Adverse Event |
| **SCC** | Squamous cell carcinoma |
| **SCCHN** | Squamous cell carcinoma of the head and neck |
| **SCCOP** | Squamous cell carcinoma of the oropharynx |
| **SD** | Stable Disease |
| **SUV** | Standardised Uptake Value |
| **tp** | Days to double cell proliferation |
| **tk** | Is the time after radiotherapy starts |
| **TDS** | Three Times Daily |
| **TMA** | Tissue Microarray |
| **TMG** | Trial Management Group |
| **TNM** | Classification of Malignant Tumours |
| **TNO** | Trial Number |
| **RNO** | Registration Number |
| **UICC TNM** | International Union Against Cancer. The TNM Classification of Malignant Tumours is a cancer staging system that describes the extent of cancer in a patient's body. T: size of the tumour and whether it has invaded nearby tissue, N: regional lymph nodes that are involved, and M: distant metastasis |
| **UK** | United Kingdom |
| **UKHAN** | UK Head and Neck |
| **WBC** | White Blood Cell |
| **WHO** | World Health Organisation |

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# 1. BACKGROUND AND RATIONALE

## 1.1 BACKGROUND

Simultaneous addition of chemotherapy to radiotherapy for squamous cell cancer of the head and neck (SCCHN) has been shown to increase overall survival. The absolute five-year survival benefit seen in a recent meta-analysis was 8% and cisplatin (cumulative dose 200mg/m$^2$) is considered to be the standard agent when used as a single agent ($p$<0.0001) (Pignon *et al.,* 2009). Due to the heterogeneity of trials using concomitant chemoradiation there is still uncertainty as to the optimum chemotherapy regime and radiotherapy fractionation.

There is a lack of standardisation of radiotherapy administered with chemotherapy around the world (Ho *et al*., 2009). Although convention is to use 2Gy fractionation over 7 weeks, a meta-analysis of 15 randomised trials with more than 5000 participants, mostly with oropharyngeal and laryngeal SCCHN, showed that altered fractionation radiotherapy yielded an absolute 5-year survival benefit of 3·4% (HR 0·92, 95% CI 0·86–0·97; $p$=0·004) (Bourrhis *et al.,* 2006). With prolonged treatment schedules radiotherapy dose has to be increased to overcome accelerated repopulation which can occur after 21 days (Roberts *et al*., 1999). Acceleration of radiotherapy refers to delivering radiotherapy in a shorter time and can overcome this effect. It has been shown to independently improve local control (Overgaard *et al., 2003*). It can be achieved in a number of ways including increasing the dose per fraction (hypofractionation). Although concerns exist over using larger doses per fraction, due to requirement for less total dose, radiobiological modelling predicts favourable late toxicity rates with equivalent local tumour control (Fowler *et al*., 2007). With shorter schedules a lower dose is required to counteract the effect of tumour cell repopulation and therefore a lower total dose can achieve equivalent tumour cell kill (Slevin *et al*., 1992). This is supported by data from retrospective series in which equivalent results to those obtained with more prolonged schedules were obtained utilizing accelerated hypofractionated schedules as short as 4 weeks (Sanghera *et al*., 2007, Gupta *et al*., 1987). Within the UK Head and Neck (UKHAN) study, a large randomised control study assessing the benefit of chemotherapy in head and neck cancer, a significant proportion of patients also received hypofractionation in schedules as short as 4 weeks (Tobias *et al.,* 2010).

Although accelerated hypofractionation has been used in head and neck cancer with synchronous chemotherapy for over 20 years, use has been confined to a few centres in the United Kingdom. Despite the more common use of 70Gy/35F with synchronous cisplatin there is no evidence to support the superiority of a 7 week course of radiation over shorter fractionation schedules.

Intensity Modulated Radiotherapy (IMRT) allows the radiotherapy dose to be precisely shaped around the tumour enabling dose reduction to specific organs at risk of damage from radiotherapy, thereby reducing toxicity (Nutting *et al.,* 2009). IMRT is becoming the standard for care for most head and neck patients and there is increasing interest in hypofractionation with this technique. Concomitant boost radiotherapy has been shown to increase locoregional control (Fu *et al.,* 2000, Ang *et al.,* 2005, Bourrhis *et al.,* 2006). With IMRT it is common practice to deliver higher doses per fraction to the tumour while delivering lower doses per fraction to the “at risk areas” over the same overall time. The ability to deliver multiple dose levels concurrently makes utilizing the radiobiological advantages of hypofractionation to the tumour more attractive as conventional doses per fraction can still be delivered to large volumes of normal tissue requiring elective radiation.

It has been possible to escalate radiotherapy dose with synchronous chemotherapy (Nutting *et al*., 2009). In the study by Nutting *et al*., two radiotherapy dose levels to macroscopic laryngeal or hypopharyngeal disease were employed: 63Gy/28F and 67.2Gy/28F. Both levels were well tolerated and locoregional control rates at 2 years were 65% vs 82% respectively. This was a non-randomised comparison. Such a dose escalation strategy has not been investigated in oropharyngeal carcinoma. Using radiobiological modelling and parameters developed by Fowler *et al.*, it is possible to compare the two dose levels used in Nutting’s study with the proposed study and other regimens (Fowler *et al*., 2007).

| Regime Gy/fractions | Overall Time (days) | Log Cell Kill | BED tumour a/b=10, tk=21, tp=3 ($Gy_{10}$) | BED mucosa a/b=10, tk=7, tp=2.5($Gy_{10}$) | BED late a/b=3 ($Gy_3$) | BED late a/b=2, ($Gy_2$) |
|---|---|---|---|---|---|---|
| 70/35 | 46 | 10.3 | 68 | 53 | 117 | 140 |
| 60/30 | 39 | 9.1 | 60 | 47 | 100 | 120 |
| 50/25 | 32 | 8.0 | 53 | 40 | 83 | 100 |
| 63/28 | 37 | 10.1 | 67 | 53 | 110 | 134 |
| *67.2/28 | 37 | 11.1 | 73 | 60 | 121 | 148 |
| †56/25 | 32 | 9.3 | 61.3 | 49 | 98 | 119 |
| 62.5/25 | 32 | 10.8 | 71 | 58 | 115 | 140 |
| 63/25 | 32 | 10.9 | 72. | 59 | 116 | 142 |
| ‡64/25 | 32 | 11.1 | 73 | 61 | 119 | 146 |
| 64.5/25 | 32 | 11.2 | 74 | 61 | 120 | 148 |

BED: Biological Effective Dose (allows comparison of different radiotherapy schedules). A value of alpha of 0.35 has been used. a/b: alpha/beta, tk: is the time after radiotherapy starts, tp: days to double cell proliferation.

*Dose escalation proved to be safe by Nutting *et al.*

†Proposed intermediate dose level.

‡Proposed high dose level.

The predictions from this modelling suggest that the high dose arm of the proposed study (highlighted) would be isoeffective, in terms of tumour cell kill, with the high dose arm of the study by Nutting *et al*. with a slightly higher predicted mucosal toxicity and lower late toxicity rate.

This modelling does not take into account the volume of normal tissue exposed to radiation. Through the increased dose conformality achieved with IMRT, the normal tissue volume surrounding the tumour exposed to a high dose of radiation can be reduced. Although most agree that a safety margin is required around the tumour (to account for tumour definition and possible microscopic disease) there is variation in practice in terms of this volume and debate as to whether it requires the same dose as the tumour (Caudell *et al.,* 2010). Dose escalation to the tumour alone, while maintaining a lower dose to surrounding tissue at risk of microscopic disease, may allow for increased tumour control without increasing toxicity.

Although escalating the dose of radiotherapy theoretically serves to increase cell kill and control, the benefit to patients remains unconfirmed and has to be balanced with any increased toxicity. Greatest therapeutic gain from dose escalation is likely to be seen in patients with a poor prognosis and it is now possible to biologically identify such patients.

Response of squamous cell carcinoma of the oropharynx (SCCOP) can now be divided into favourable and poor prognostic groups according to whether or not there is association with Human Papillomavirus (HPV). HPV status of SCCOP can now be accurately defined using a combination of high risk HPV *in situ* hybridisation and P16 expression by immunohistochemistry (Singhi and Westra, 2010). Such a technique was used by Ang *et al* for patients within the Radiation Therapy Oncology Group *(*RTOG) 0129 study to confirm the prognostic effect of HPV. The 3 year overall survival for HPV negative tumours treated with chemoradiation within the RTOG 0129 was only 57.1% compared to 82.4% ($p<0.001$) for HPV positive tumours (Ang NEJM 2010)). The 3 year progression free survival was 43.4%, versus 73.7% for HPV negative and positive tumours respectively, and the effect of HPV status was predominantly on locoregional control. Within the study patients with HPV positive tumours and a history of smoking (>10 pack years) also had a worse prognosis. Patients could be categorised according to HPV and smoking status creating high risk, intermediate and low risk groups. Patients with HPV positive cancer and a >10 pack year history of smoking had a similar prognosis to patients with HPV negative T2-3 tumours and <10 pack year history of smoking (3 year overall survival 70.8%).

Although there is interest in reducing the intensity of treatment in patients with HPV positive SCCOP, HPV negative SCCOP patients and HPV positive heavy smokers remain common in the UK and due to poor local control rates warrant a more aggressive treatment approach such as dose escalation. Furthermore, HPV negative tumours are more typically seen in elderly male smokers and this group often suffers with poor compliance. A shorter schedule may also help improve outcome through better compliance for this group of patients.

The purpose of the proposed feasibility study is to investigate the feasibility and safety of administering a dose of 64Gy/25F to macroscopic tumour with cisplatin chemotherapy in patients with poor prognosis squamous cell carcinoma of the orophayrnx. This is prior to investigation in a randomised study comparing with a 7 week standard dose schedule.

## 1.2 STUDY RATIONALE

### 1.2.1 Justification for patient population

SCCOP that are HPV negative and P16 negative have a high risk of local disease relapse following conventional dose radiotherapy with concurrent chemotherapy. These tumours typically occur in a patient group that suffers with a poor compliance to 7 weeks of radiotherapy. Patients with stage N2b-3 HPV positive tumours and a greater >10 pack year history of smoking also have a high risk of local failure (similar to HPV negative T2-3 tumours in patients with <10 pack year history of smoking). This group currently forms the group of patients that are not being evaluated in the DeESCALATE study due to high risks of recurrence.

The purpose of the proposed feasibility study is to investigate the feasibility and safety of administering a dose of 64Gy/25F to macroscopic tumour with cisplatin chemotherapy in patients with poor prognosis SCCOP. This is prior to investigation in a randomised study comparing with a 7 week standard dose schedule.

### 1.2.2 Justification of design

This is a single centre, single arm feasibility study registering 15 patients with locally advanced SCCOP. The intervention period will be 5 weeks. Patients will be followed up for 5 years in order to determine toxicity, local control, disease free survival, overall survival and late toxicity.

### 1.2.3 Choice of treatment

IMRT 64Gy/25F to the primary tumour and involved nodes with elective irradiation of clinically uninvolved nodes to a dose of 50Gy/25F. An intermediate dose of 56Gy/25F will be delivered to regions deemed at high risk of microscopic disease (this will include anatomical regions at high risk of disease).

The treatment period includes:

- 1 treatment a day for 32 days (5 weeks) excluding Saturdays and Sundays
- Treatment should be completed within 32 days which will require compensation for any breaks in treatment due to logistics (for example, machine breakdown)

Chemotherapy (Cisplatin) given as standard care:

- Dose: Cisplatin 100 mg/m$^2$
- Dosing schedule: Cisplatin 100 mg/m$^2$ will be administered on day 1 of week 1 and day 1 of week 5
- If cisplatin is contra-indicated (e.g renal impairment), Carboplatin AUC 5 week 1 and 5 will be used consistent with standard care

# 2. AIMS, OBJECTIVES AND OUTCOME MEASURES

## 2.1 AIMS AND OBJECTIVES

To determine whether it is safe and feasible to deliver a 5 week schedule of dose escalated IMRT for poor prognosis patients with locally advanced SCCOP

## 2.2 OUTCOME MEASURES

### 2.2.1 Primary outcome measures

- Full dose radiotherapy received as planned and the absence of consequential damage: defined by the absence of Grade 3 mucositis at 3 months

### 2.2.2 Secondary outcome measures

- Duration of Grade 3 mucositis: defined as the number of days of Grade 3 mucositis scored using National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 3 (see appendix 1)
- Incidence of acute Grade 4 toxicity defined according to the NCI CTCAE version 4 (see appendix 1)
- Incidence of ≥ Grade 3 late toxicity defined according to RTOG (see appendix 2) and CTCAE version 4 scoring systems
- Complete response rate at 3 months defined as no clinically visible (including endoscopic evaluation), palpable or measurable disease on imaging OR the absence of residual tumour on directed biopsy/neck dissection. The primary tumour and regional lymph nodes will be considered separately
- 2 year local control defined as no re-appearance of tumour within primary site (including immediately adjoining anatomical sites) or regional lymph nodes after complete response
- 2 year disease free survival defined in whole days, as the time from entry into the study until death from any cause. Patients will be censored at the date last seen alive. All patients will be followed up for at least 5-years
- 2 year overall survival defined in whole days as the time from entry into the study until death from any cause. Patients will be censored at the date last seen alive. All patients will be followed up for at least 5-years
- Incidence of feeding tube dependency at one year defined by the patient requiring supplementation of nutrition by a feeding tube

## 3. STUDY DESIGN

This is a single-centre, single-arm, feasibility study registering 15 patients with locally advanced SCCOP. The intervention period will be 5 weeks. Patients will be followed up for 5 years in order to determine toxicity, local control, disease free survival, overall survival and late toxicity.

**Obtain Consent for Screening**

**Registration for screening**
Patients registered onto the study will be allocated a Registration Number (RNO)
Tel: 0800 371 969 (9:00am till 5:00pm Monday to Friday)

**Patients screened for HPV and P16**
Send slides and tissue blocks to Department of Cellular Pathology, Newcastle-Upon-Tyne Hospitals NHS Foundation Trust

**Confirm Eligibility**

**Obtain Consent for Study Entry**

**Study Entry**
Patients entered onto the study subject to successful screening, Patient will be allocated a Trial Number (TNO)
Tel: 0800 371 969 (9:00am till 5:00pm Monday to Friday)

**Treatment**
IMRT 64Gy in 25F for 32 days (dose to primary tumour and involved nodes)
+
Cisplatin 100 mg/m$^2$ week 1 and week 5

**Early Follow-up:**

- Weekly during radiotherapy
- Weekly for first 6 weeks or until resolution of Grade 3 mucositis

**5 Year Follow-up & Toxicity Response:**

- Local control assessment at 3 months
- MRI scan at 3 months and biopsy of primary site and/or neck dissection as indicated
- Further surveillance follow-up according to local follow-up guidelines including documentation of local control and disease free survival at 12 and 24 months
- Toxicity assessments at 3, 6, 12, 18, 24, 36, 48 and 60 months

# 4. ELIGIBILITY

## 4.1 INCLUSION CRITERIA

1. Histologically proven HPV and P16 negative SCCOP deemed suitable for radical primary chemoradiotherapy with curative intent requiring bilateral neck radiotherapy or patients with P16 positive tumours if stage N2b-3 and greater than 10 pack year history of smoking. Neoadjuvant chemotherapy and pre or post chemoradiation neck dissections are permitted.
2. Only patients requiring bilateral radiotherapy
3. Age ≥18 and <75 years
4. World Health Organisation (WHO) Performance Status 0 or 1 (see appendix 3)
5. Adequate bone marrow : absolute neutrophil count > 1,800 cells/$mm^3$, platelets > 100,000 cells/$mm^3$, Haemoglobin > 8.0 g/dl
6. Creatinine clearance > 50ml/minute
7. Informed consent

Clinical and pathological staging is performed according to the International Union Against Cancer, Classification of Malignant Tumours Staging Manual (UICC TNM) (see appendix 4).

## 4.2 EXCLUSION CRITERIA

1. Prior invasive malignancy (except base cell carcinoma and cervical intraepithelial neoplasia) within last 3 years
2. Prior radiotherapy to the head and neck region
3. Pregnancy and/or lactation
4. Reproductive capability and dis-agreement to use contraceptive
5. Contraindications to cisplatin and carboplatin chemotherapy including active vascular disease (e.g. myocardial within last 6 months, angina and symptomatic peripheral vascular disease)
6. Non curative intent
7. Non squamous carcinoma histology
8. Nasopharynx, larynx, hypopharynx, salivary gland or sino-nasal primary site
9. Other physical or psychiatric disorder that may interfere with subject compliance, adequate informed consent, follow-up or determine the causality of adverse events
10. Suitable for unilateral radiotherapy

# 5. PATIENT SCREENING, INFORMED CONSENT AND REGISTRATION

Potential patients will be recruited if they have locally advanced SCCOP and require chemoradiotherapy with curative intent involving both sides of the neck.

These patients will be identified at the head and neck Multidisciplinary Team (MDT) meeting within University Hospitals Birmingham NHS Foundation Trust from oncology clinics and invited to take part in the study. As part of the screening process and to confirm eligibility, patients will be screened for P16 as a standard procedure and for HPV after patient consent for HPV screening has been obtained. Only patients meeting the eligibility criteria will be entered into the ArChIMEDEs-Op Study. Eligibility will be determined according to the pathway outlined in section 5.2.1

## 5.1 INFORMED CONSENT AND REGISTRATION

It is the responsibility of the Investigator to obtain written informed consent for each patient prior to performing any study related procedure. A Patient Information Sheet is provided to facilitate this process. Investigators must ensure that they adequately explain the aim, study treatment, anticipated benefits and potential hazards of taking part in the study to the patient. The Investigator should also stress that the patient is completely free to refuse to take part or withdraw from the study at any time. The patient should be given ample time (24 hours) to read the Patient Information Sheet and to discuss their participation with others outside of the site research team. The patient must be given an opportunity to ask questions which should be answered to their satisfaction. The right of the patient to refuse to participate in the study without giving a reason must be respected.

### 5.1.1 Screening

If the patient expresses an interest in participating in the ArChIMEDEs-Op study, further arrangements will be made for P16 and HPV screening. Patients will be screened for HPV after patient consent has been obtained using the ArChIMEDEs-Op Screening Informed Consent Form. Prior to performing any screening assessments, patients will be registered into the ArChIMEDEs-Op study and assigned a screening Registration Number (RNO) which should be recorded on the ArChIMEDEs-Op Screening Informed Consent Form maintained in the Investigator Site File (ISF). Both the participant and the Investigator should be asked to sign and date the latest version of the ArChIMEDEs-Op Screening Informed Consent Form. In addition, if the patient has given explicit consent, a copy of the signed ArChIMEDEs-Op Screening Informed Consent Form must be sent in the post to the ArChIMEDEs-Op Study Office for review.

Following screening, patients with HPV and P16 negative SCCOP or patients with P16 positive tumours if stage N2b-3 and greater than 10 pack year history of smoking will be eligible. Patients with stage N2b-3 SCCOP and greater than 10 pack year history of smoking can consent for the study prior to central review of pathology. These patients will be invited back to clinic and asked if they would like to participate in the study.

### 5.1.2 Study Entry

Written informed consent for study entry will be obtained using the ArChIMEDEs-Op Study Entry Informed Consent Form, provided the patient is willing to take part in the study, has had all the questions answered satisfactorily and has read the Patient Information Sheet. Both the participant and the Investigator are required to sign and date the latest version of the ArChIMEDEs-Op Study Entry Informed Consent Form. Once the patient is entered into the study, the patient will be assigned a unique Trial Number (TNO) which should be recorded on the ArChIMEDEs-Op Study Entry Informed Consent Form maintained in the ISF. In addition, if the patient has given explicit consent, a copy of the signed ArChIMEDEs-Op Study Entry Informed Consent Form must be sent in the post to the ArChIMEDEs-Op Study Office for review.

A copy of the ArChIMEDEs-Op Screening Informed Consent Form and ArChIMEDEs-Op Study Entry Informed Consent Form should be given to the patient, a copy should be filed in the hospital notes, and the originals placed in the ISF. Details of the informed consent discussions should be recorded in the patient's medical notes, this should include date of, and information regarding, the initial discussion, the date consent was given, with the name of the study and the version number of the Patient Information Sheet and Informed Consent Forms. Throughout the study the patient should have the opportunity to ask questions about the study and any new information that may be relevant to the patient's continued participation should be shared with them in a timely manner. On occasions it may be necessary to re-consent the patient in which case the process above should be followed and the patient's right to withdraw from the study respected.

Electronic copies of the Patient Information Sheet and Informed Consent Forms are available from the ArChIMEDEs-Op Study Office and should be printed or photocopied onto the headed paper of the local institution.

Details of all patients approached about the study should be recorded on the Screening Log and with the patient's prior consent their General Practitioner (GP) should also be informed that they are taking part in the study. A GP Letter is provided electronically for this purpose.

### 5.1.3 Screening Registration

To register a patient for screening, Investigators should complete a Registration Form and call the ArChIMEDEs-Op Study Office on:

**To register a patient for screening, telephone 0800 371 969**

**Monday to Friday, 9:00am till 5:00pm**

During the registration procedure verification that the patient has signed the ArChIMEDEs-Op Screening Informed Consent Form will be requested. In addition, the patient's initials, date of birth, hospital number as well as the name of hospital and name of Investigator directly responsible for the patient's care will be requested. Investigators must be registered with the ArChIMEDEs-Op Study Office before they are permitted to register patients into the study.

At the end of the screening registration process, the patient will be assigned a unique RNO. The RNO will only be used to identify patient samples and Pathology Reports sent to Pathology Department, Department of Cellular Pathology, Royal Victoria Infirmary for screening. The completed Registration Form and a copy of the ArChIMEDEs-Op Screening Informed Consent Form and Pathology Report should also be sent to the ArChIMEDEs-Op Study Office in the post. Patient identifiable information (patient's name, date of birth, hospital number etc) should be removed from the Pathology Reports and the patient's RNO and initials should be written on the report for identification purposes.

## 5.2 SCREENING

Screening procedures described in section 5.2.1 should be undertaken. Prior to performing any screening procedures, the Investigator will provide information about the study to allow them to make an informed decision regarding their participation. If informed consent for screening is given, the Investigator will conduct a full screening evaluation to ensure that the patient satisfies all inclusion and exclusion criteria. For patients who meet the inclusion criteria and have given written informed consent for study entry may be entered into the study.

Investigators will be expected to maintain details of all patients approached about the study on the Screening Log. This Log will include limited information about the patient (i.e. date of birth), date and outcome of the screening process (e.g. registered into study, reason for ineligibility, or refused to participate). The Screening Log will be reviewed by the ArChIMEDEs-Op Study Office in order to monitor recruitment and identify issues with eligibility.

### 5.2.1 Pathway for determining HPV and P16 status

Tissue samples will be collected from patients that have consented for screening prior to study entry. Sections from the diagnostic core biopsy (6 x 5 µm stained sections) will be mounted on superfrost plus slides. Each tissue sample section and the corresponding Pathology Report will be identified by the screening RNO. The tissue sample sections, section 1 of the 3-part Tissue Sample Shipment Confirmation Form and a copy of the Pathology Report will be sent to the Department of Cellular Pathology, Royal Victoria Hospital, Newcastle-upon-Tyne Hospitals Foundation Trust for molecular classification. Section 2 of the 3-part Tissue Sample Shipment Confirmation Form will be sent to the ArChIMEDEs-Op Study Office. Section 3 of the 3-part Tissue Sample Shipment Confirmation Form will be retained in the Human Biomaterial Resource Centre (HBRC), University Hospitals Birmingham NHS Foundation Trust. The shipment of tissue samples sections to the Department of Cellular Pathology will be tracked using an in-house Tissue Sample Log by ArChIMEDEs-Op Study Office. The contact details and address for dispatch are as follows:

Dr Max Robinson (Consultant in Oral Pathology)
Department of Cellular Pathology
Royal Victoria Infirmary
Queen Victoria Road
Newcastle Upon Tyne
Tyne and Wear
NE1 4LP

Tel: 0191 282 4445
Fax: 0191 282 5892

Following screening, the tissue section slides will be stored at Pathology Department, Department of Cellular Pathology, Royal Victoria Infirmary for the duration of the study. At the end of the study, the samples will be destroyed by the Royal Victoria Infirmary, Pathology Department according to their local policy.

#### *5.2.1.1 P16 Immunohistochemistry*

P16 immunohistochemistry will be carried out using a proprietary kit (CINtec histology, MTM laboratories AG, Germany) on the Ventana Benchmark XT Autostainer (Ventana Medical Systems Inc, USA). Test cases will be compared with a high risk HPV positive OPSCC that shows high P16 expression (positive control). The primary antibody will be omitted from negative controls. The P16 test will be interpreted independently by two pathologists. The P16 test will be scored as positive if there is strong and diffuse nuclear and cytoplasmic staining present in greater than 70% of the tumour specimen. All other staining patterns will be scored as negative. In cases where the interpretation differs between the two pathologists, the slides will be re-examined and a consensus reached.

#### *5.2.1.2 High risk HPV in situ hybridisation*

High risk HPV *in situ* hybridisation will be carried out using a proprietary kit (Inform HPV II, Ventana Medical Systems Inc, USA) on the Ventana Benchmark XT Autostainer (Ventana Medical Systems Inc, USA). The Inform HPV II Family 16 Probe (B) detects a range of high risk genotypes 16, 18, 31, 33, 35, 39, 51, 52, 56, 58 and 66. Test cases will be compared with three control samples; formalin fixed paraffin embedded cell line 'buttons' of CaSki cells (HPV-16 positive; 600 copies per cell), HeLa (HPV-18 positive; 10-50 copies per cell) and an HPV negative cell line (Ventana Medical Systems Inc, USA). Test cases will be compared with a high risk HPV positive OPSCC (positive control) and a HPV negative OPSCC (negative control). The HPV test will be interpreted independently by two pathologists. The HPV test will be scored as positive if there is evidence of a blue reaction product that co-localises with the nuclei of malignant cells. In cases where the interpretation differs between the two pathologists, the slides will be re-examined and a consensus reached.

#### *5.2.1.3 Quality Assurance and Test Interpretation*

This diagnostic pathway forms part of the routine diagnostic service in the Department of Cellular Pathology, Royal Victoria Infirmary, Newcastle-upon-Tyne Hospitals Foundation Trust. The tests are CE-marked for diagnostic purposes, are subject to laboratory quality assurance and form part of a Clinical Pathology Accreditation (CPA (UK) Ltd) approved diagnostic service. The tests were introduced in the laboratories in June 2009 and to date have analysed over 250 cases of which 90 cases have been audited (Thavaraj et al., 2011). Three pathologists (Dr Max Robinson, Dr Atuora Okpokam and Professor Philip Sloan) deliver the head and neck pathology specialist service at Newcastle-upon-Tyne Hospitals Foundation Trust and all have accumulated experience of interpreting the tests. There is high inter-observer correlation between the pathologists (Intraclass correlation 0.964; 95% CI 0.949-0.975; $p<0.001$). The involvement of three pathologists at one site means that delivering the diagnostic protocol is feasible. The quality objective is to provide the HPV status within 3 working days from receipt of the unstained slides. We will audit the accrual of study material against this quality object and seek feedback from the participating centres.

A case that shows evidence of HPV DNA by high risk HPV *in situ* hybridisation and shows high P16 expression by immunohistochemistry will be defined as harbouring biologically relevant high risk HPV infection and will be classified as 'HPV positive oropharyngeal SCC' (HPV+/P16+).

### 5.3.2 Timeline

**Day 1**

- Tissue sections, Tissue Sample Shipment Confirmation Form and Pathology Report received by the medical secretaries at the Department of Cellular Pathology, Royal Victoria Infirmary, Newcastle-upon-Tyne Hospitals Foundation Trust
- Medical secretary logs the case on the iLAB Pathology System (patient initials and screening registration number)
- Case allocated to Dr Max Robinson
- The sections are despatched to the Immunohistochemistry Laboratory with a completed supplementary request form
- Booking form and original Pathology Report despatched to Dr Max Robinson
- Immunohistochemistry laboratory, sections received with supplementary request form
- Slides stained for:
  - Haematoxylin and eosin (H&E)
  - P16 immunohistochemistry: P16 test with De-Escalate HPV control TMA on slide
  - High risk HPV in situ hybridisation (HR-HPV ISH): HR HPV ISH test with De-Escalate HPV control TMA on slide
- Staining protocol completed the same day or using an overnight program

**Day2**

- Sections despatched to Dr Max Robinson for interpretation
- Sections passed to second pathologist (Professor Philip Sloan or Dr Atuora Okpokam) for interpretation
- Consensus interpretation and final report composed in iLAB Pathology System
- Result anonymised and communicated by secure FAX to Research Office, University Hospitals Birmingham NHS Foundation Trust
- Original Pathology Report returned to University Hospitals Birmingham NHS Foundation Trust. Stained slides stored at Department of Cellular Pathology, Royal Victoria Infirmary

## 6. STUDY ENTRY

Once the patient has signed the ArChIMEDEs-Op Study Entry Informed Consent Form, and their eligibility has been confirmed through the screening assessments, an Eligibility Form and a Study Entry Form must be completed. These details should be telephoned through to the Cancer Research UK Clinical Trials Unit (CRCTU), University of Birmingham. The completed Eligibility Form and a Study Entry Form should be sent in the post to the ArChIMEDEs-Op Study Office as soon as possible after the patient has been entered into the study. To enter a patient into the study call:

**To enter patient, telephone 0800 371 969**

**Monday to Friday, 9:00am till 5:00pm**

The Investigator will be asked to confirm patient's details and all the information requested on the Study Entry Form should be provided. This will include:

- Patient's initials and date of birth
- Screening Registration Number
- Verification that patient has signed the ArChIMEDEs-Op Study Entry Informed Consent Form
- Confirmation of eligibility criteria and verification of screening results

Following study entry registration, patient will be assigned a unique TNO. This allocated number should be recorded on the Eligibility Form, Case Report Forms (CRF) and all subsequent correspondence relating to the patient for the ArChIMEDEs-Op study. The completed original CRFs should be sent to the ArChIMEDEs-Op Study Office in the post with copies retained at site.

# 7. STUDY TREATMENT

## 7.1 INTENSITY MODULATED RADIOTHERAPY PLANNING

### 7.1.1 Immobilisation

All patients will be immobilised in a custom made thermoplastic shell that encompasses head and shoulders according to each departmental protocol for head and neck IMRT patients. The immobilisation should remain consistent.

### 7.1.2 Planning Computer Tomography

- All patients should have intravenous (IV) contrast (100 ml Omnipaque) unless contra-indicated
- 2-3 mm axial slices are recommended
- Total scan length should include supra orbital ridge to 2 cm below carina
- Where required, bolus should be applied at the time of immobilisation

### 7.1.3 Image Fusion

- Fusion of diagnostic scans including Computed Tomography (CT), Magnetic Resonance Imaging (MRI) and Position Emission Tomography (PET) is recommended
- When neoadjuvant chemotherapy is used, patients should have diagnostic pre-chemotherapy cross sectional imaging fused with the planning CT scan

### 7.1.4 Dose Prescription

- 64Gy/25F: Primary tumour/involved nodes
- 56Gy/25F: Intermediate dose for regions at high risk of microscopic disease (e.g. immediately adjacent anatomical region/post neck dissection surgical bed)
- 50Gy/25F: Prophylactic dose (e.g. uninvolved nodes at a lower risk of involvement)
- Fractions will be delivered once daily Monday to Friday with the aim of completing within 32 days (5 weeks)

### 7.1.5 Countering

- Gross Tumour Volume (GTVp): Primary tumour delineated based on pre-induction chemotherapy diagnostic imaging, clinical assessment and contrast enhanced planning CT scan
- Gross Tumour Volume (GTVn) : Involved nodes
- All defined Clinical Target Volumes (CTVs) and Planning Target Volumes (PTVs) should be followed by the intended dosage e.g. PTV64

Refer to RTOG guidelines for delineation of lymph node levels (the guidelines for CT based delineation of lymph node levels can be found at the RTOG website: http://www.rtog.org/hnatlas/main.html). Published guidelines for nodal target volume delineation in patients that are node positive, or in those that have had a neck dissection should be referred to guidelines by Gregoire V *et al.,* 2006.

### 7.1.6 Clinical Target Volume (CTV64)

- CTV64 should include GTVp + GTVn and includes an allowance for uncertainty in delineating gross tumour
- CTV64 = GTVp + minimum 5 mm margin respecting anatomical borders where appropriate [e.g. do not contour through bone (unless invaded) or airspace]. This may be increased (for example, 1 cm) if the clinician considers there is uncertainty in gross tumour definition
- + GTVn + minimum 0.5 cm (extending to at least 1 cm if risk of extra capsular spread). Where lymph nodes abuts soft tissue (e.g. muscles) or where there is bulky/extensive nodal disease, suspicion of soft tissue infiltration around the node or significant changes in volume post induction chemotherapy, an additional margin is required to include contiguous soft tissues at least within that nodal level. Beyond this abutting muscles should be included within the CTV56 for a minimum of 2 cm

### 7.1.7 Clinical Target Volume (CTV56)

Regions anticipated to a have high risk of microscopic spread including:

- Postoperative bed following a neck dissection
- Anatomical regions adjacent to primary at high risk of disease. This should include ipsilateral oropharynx, parapharygeal space and a minimum margin of **10 mm** surrounding the GTV (modified according to anatomical boundaries to tumour spread). For tumours with infiltrating, uncertain margins the CTV56 can be increased up to 20 mm.
- First station lymph nodes

### 7.1.8 Clinical Target Volume (CTV50)

Regions anticipated to have a lower risk of microscopic disease:

- Contralateral oropharynx not encompassed in CTV 64 or 56
- Contralateral parapharyngeal space
- Uninvolved nodes at risk of microscopic spread:
    - N0: ipsilateral 1b, II-V, contralateral Ib-III, bilateral retropharyngeal at the level of the oropharynx
    - N +ve: ipsilateral Ib-V, ipsilateral supraclavicular fossa, contralateral Ib-IV, bilateral retropharyngeal nodes to skull base

### 7.1.9 Planning Target Volumes (PTV64/56/50)

- These represent an additional margin around each CTV to compensate for the variability of treatment set up and internal organ motion. An isotropic margin of 3-5 mm around the CTV is anticipated (e.g. PTV64 = CTV 64 + 0.5 cm) and this is defined according to individual department data on accuracy of immobilisation. In situations in which the CTV is adjacent to spinal cord or other critical normal tissues judicial reduction is allowed. When PTVs overlap, the higher dose has a higher priority
- Skin margins should be automatically trimmed by 5 mm
- When tumour lies close to skin, bolus should be used to build up the dose. Do not attempt to use IMRT to deliver a high skin dose

### 7.1.10 Intensity Modulated Radiotherapy Planning

Inverse planned IMRT using existing planning software meeting specified constraints and planning targets outlined below. The planning technique can vary according to available IMRT software but should be recorded.

### 7.1.11 Normal Tissue Constraints

- All constraints are calculated for this 25F schedule
- All serial organs should have a margin for planning risk margin according to local data

| ORGAN | Volume Constraint | Dose Constraint (Gray) | PRIORITY |
|---|---|---|---|
| PRV spinal cord | Max | 45 | Absolute |
| PRV brainstem | Max | 50 | Absolute |
| PRV brainstem | 1cc | 48 | Absolute |
| Brain | Max | 60 | Absolute |
| Brain | 1cc | 58 | Absolute |
| PRV Chiasm | Max | 50 | Absolute |
| PRV Optic nerves | Max | 50 | Absolute |
| Globes | Max | 40 | Absolute |
| Contralateral parotid (unedited) | Mean | 24Gy (mean) | Recommended |
| *Bilateral Superficial Parotid | Mean | 24Gy (mean) | Recommended |
| Lips | Max | 35 | Recommended |
| Mandible (edited) | Max | 64 | Recommended |
| Larynx (edited) | | 45 | Recommended |
| Lens | Max | 5 | Recommended |
| Cochlea PRV | Mean | 35 | Recommended |
| Brachial Plexus PRV | Max | 56 | Recommended |

All neural tissue constraints need to be respected with high priority. The brachial plexus dose applies providing the CTV does not the brachial plexus planning organ at risk volume (PRV). For disease abutting the brachial plexus this limit will have to be exceeded consenting for the increased risk.

*For midline tumours the bilateral superficial parotid dose constraint should be used rather than the contralateral parotid.

### 7.1.12 PTV Dose Limits and Reporting

The prescription will be to the median dose point on the Dose Volume Histograms (DVH) such that the prescription dose (64Gy) is received by 50% of the PTV64.

| | | PTV 64 | | PTV 56 | | PTV 50 | |
|---|---|---|---|---|---|---|---|
| **% Volume** | **% Dose** | Dose Required | Dose Achieved | Dose Required | Dose Achieved | Dose Required | Dose Achieved |
| **99%** | **>90%** | 57.6 | | 50.4 | | 45.0 | |
| **95%** | **>95%** | 60.8 | | 53.2 | | 47.5 | |
| **50%** | **=100%** | 64.0 | | 56.0 | | 50.0 | |
| **5%** | **<105%** | 67.2 | | 58.8 | | 52.5 | |
| **2%** | **<110%** | 70.4 | | 61.6 | | 55.0 | |

***Absolute dose limit not to be exceeded.**

No more than 1 cc of normal tissue to receive >110% of prescribed dose. In selected circumstances deviations from the above may be required but these should be reported and justified.

### 7.1.13 Radiotherapy Planning Protocol Deviations

All deviations from above dose metrics should be reported using the Deviation Form and justified. Any deviations of absolute dose constraints / limits require reporting prior to treatment commencement and will be considered major protocol deviation.

## 7.2 INTENSITY MODULATED RADIOTHERAPY DELIVERY

### 7.2.1 Treatment Schedule

Treatment should begin within 3-4 weeks of consenting to the study and within 8 weeks from diagnosis unless the patient is having neo-adjuvant chemotherapy in which radiotherapy will commence following induction chemotherapy. The planned duration of treatment is 5 weeks. Radiotherapy should commence on a Monday. If radiotherapy cannot be started on a Monday, compensation in the form of a Saturday treatment or double treatments within one day is required.

### 7.2.2 Verification of Dose Delivery

Departmental IMRT quality assurance procedures must be in place and adhered to for all patients.

### 7.2.3 On-Treatment Verification

Institutional imaging verification for head and neck patients receiving IMRT should be in place and adhered to. A minimum of weekly on treatment imaging verification is required. Both online and offline position corrections are permitted. A local policy should be in place to deal with weight changes leading to movement beyond local tolerance. This should enable early identification of such patients and re-planning if necessary without a treatment break.

Adaptive planning based on soft tissues changes detected through 3 dimensional imaging is permitted. All re-plans should be reported with clear documentation on the reason for change. Any re-evaluation during treatment should also be reported with documentation of alteration in dose metrics.

### 7.2.4 Radiotherapy Treatment

Intensity Modulated Radiotherapy (IMRT) 64Gy/25F to the primary tumour and involved nodes with elective irradiation of clinically uninvolved nodes to a dose of 50Gy/25F. An intermediate dose of 56Gy/25F will be delivered to regions deemed at high risk of microscopic disease (this will include anatomical regions at high risk of disease). Treatment period includes:

- 1 treatment a day for 32 days excluding Saturdays and Sundays (5 weeks)
- Treatment should be completed within 32 days which will require compensation for any breaks in treatment due to logistics (for example, machine break down) consistent with Royal College of Radiologists (RCR) guidelines

## 7.3 CHEMOTHERAPY DELIVERY

### 7.3.1 Optional Induction Chemotherapy

2-3 cycles of induction Chemotherapy are permitted as per local policy.

### 7.3.2 Concurrent Chemotherapy

Chemotherapy (Cisplatin) will be given as standard care.

- Dose: Cisplatin 100 mg/$m^2$
- Dosing schedule: Cisplatin 100 mg/$m^2$ will be administered on day 1 of week 1 and day 1 week 5
- Route/mode of administration: Intravenous
- Dexamethasone 8mg and Ondansetron 8 mg will be administered intravenously as anti-emetics. Aprepitant 125 mg PO day 1 and 80 mg PO day 2 and 3 (repeated days 29-31) will also be administered
- Dexamethasone 2 mg tds and Domperidone 10 mg qds (in tablet or suspension) will be issued as take home anti-emetics

It is anticipated that the patient will be reviewed prior to the second cycle of Cisplatin. Any dose modification or omission due to toxicity should be recorded. If the patient develops renal failure or neuropathy, Cisplatin can be replaced with Carboplatin. If contraindications to Cisplatin chemotherapy then Carboplatin AUC 5 may be used week 1 and 5, as per standard practice.

## 7.4 DOSE MODIFICATION & RADIOTHERAPY TREATMENT BREAKS

Treatment breaks are only allowed for severe acute toxicity or intercurrent illness and not social or logistical reasons. Any radiotherapy treatment break due to toxicity should be reported with documentation of reasons. Cisplatin administration will be according to local standard practice and dose modification, delay or omission should be reported on the Radiotherapy Treatment Form.

## 7.5 BREAKDOWN AND SERVICE DAY POLICY

All patients are category 1 and will require compensation for gaps according to RCR guidelines. Any extension in overall treatment time due to logistical reasons (e.g. service day) will be considered a protocol deviation and should be reported on the Deviation Form. Should a gap occur due to inter-current illness or acute toxicity, compensation should be considered if safe to enable completion on time. If required, 2 fractions per day are permitted with a minimum inter-fraction interval of 6 hours.

## 7.6 RADIOTHERAPY COMPLIANCE

Compliance to radiotherapy should be reported. Any radiotherapy treatment break/prolongation of overall treatment time for causes other than acute toxicity or inter-current illness will be considered a protocol deviation and should be reported on the Post Radiotherapy Compliance Form and Deviation Form.

## 7.7 RADIOTHERAPY QUALITY ASSURANCE

Contouring / Plan review: All patients require contouring and plan review by two Investigators (Consultants) and relevant deviations should be reported on the Deviation Form.

## 7.8 PATIENT WITHDRAWAL

Patients are free to withdraw from the study at any time. In the event of a patient's decision to withdraw from the study, the Investigator should ascertain from which aspects of the study the patient wishes to withdraw (see below). The details of patient withdrawal (date and reasons for withdrawal) should be clearly documented in the source data. A Withdrawal Form should be completed and returned to the ArChIMEDEs-Op Study Office.

- The patient would like to withdraw from study medication, but is willing to be followed up according with the schedule of assessments (i.e. the patient has agreed that data can be collected and used in the trial analysis)

- The patient would like to withdraw from study medication and does not wish to attend study visits in accordance with the schedule of assessments but is willing to be followed up at standard clinic visits (i.e. the patient has agreed that data can be collected at standard clinic visits and used in the trial analysis

- The patient would like to withdraw from study medication and is not willing to be followed up for the purposes of the trial at any further visits (i.e. only data collected prior to the withdrawal of consent can be used in the trial analysis)

# 8. SCHEDULE OF ASSESSMENTS

## 8.1 SCREENING ASSESSMENT

Patients will be recruited if they have locally advanced SCCOP, confirmed on biopsy. Only patients requiring bilateral neck radiotherapy will be suitable.

## 8.2 BASELINE ASSESSMENT

- Physical examination including endoscopic examination of the primary site with biopsy. In most cases this will require examination under general anaesthetic
- Weight and WHO performance status
- Urea, creatinine, sodium, potassium, magnesium
- Glomerular Filtration Rate
- Haemoglobin, white blood cell and platelet counts
- Liver Function Tests
- CT scan and MRI scan of primary site and neck
- CT scan chest
- Dietary assessment (including assessment for percutaneous feeding tube)
- Dental assessment

## 8.3 ON TREATMENT ASSESSMENT

Clinical evaluation will be performed weekly during radiotherapy or until resolution of Grade 3 mucositis according to the NCI CTCAE version 3. The NCI CTCAE version 4.0 toxicity scale will be used to grade acute side effects. Full blood count, urea, electrolytes and creatinine will be performed weekly during radiotherapy. Dietary assessment will also be performed weekly during radiotherapy.

## 8.4 FOLLOW-UP ASSESSMENTS

All patients, provided that they have not withdrawn consent to follow-up, should have long-term follow-up of at least 5 years, irrespective of whether they discontinued study treatment prematurely. The anticipated frequency is:

**Early Post Radiotherapy Follow-up:**

- Weekly follow-up and documentation of acute toxicity for a minimum of 6 weeks post radiotherapy or until resolution of Grade 3 mucositis

**Late Follow-up and Response Assessment:**

- Local control documentation at 3 months determined by clinical evaluation (including nasoendoscopy) and MRI scan of head and neck. Directed biopsy should be performed in patients with suspicion of local residual disease and a neck dissection is required for patients with persistent neck disease (clinical or radiological suspicion)
- Thereafter, follow-up according to established local protocols (for example, monthly for the 1$^{st}$ year and every 8 weeks for the 2$^{nd}$ year)
- Documentation of local control and disease free survival is required at 12 and 24 months
- Late toxicity assessment will be recorded at 3, 6, 12, 18, 24 36, 48 and 60 months using NCI CTCAE version 4 and RTOG scoring systems

**SCHEDULE OF EVENTS FLOWCHART**

| Assessment | Screening | Pre-study Entry | Pre-radiotherapy | During Radiotherapy (week) | | | | | Early Post Treatment (week) | | | | | | | Long term follow up (month) | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 3 | 6 | 12 | 18 | 24 | 36 | 48 | 60 |
| Obtain consent | x | x | | | | | | | | | | | | | | | | | | | | | |
| Confirm Eligibility (including CXR;FBC;CrCl) | x | x | | | | | | | | | | | | | | | | | | | | | |
| Histology report including p16 and HPV | | x | | | | | | | | | | | | | | | | | | | | | |
| Staging CT/MRI H&N | | x | | | | | | | | | | | | | | | | | | | | | |
| Dental assessment | | | x | | | | | | | | | | | | | | | | | | | | |
| Nutrition assessment | | | x | x | x | x | x | x | | | | | | | | | | | | | | | |
| Plan evaluation | | | x | | | | | | | | | | | | | | | | | | | | |
| Baseline toxicity | | | x | | | | | | | | | | | | | | | | | | | | |
| Acute toxicity | | | | | x | x | x | x | x | x | x | x | x | x | x | | | | | | | | |
| Chemotherapy and Radiotherapy compliance | | | | | | | | | x | | | | | | | | | | | | | | |
| Late toxicity | | | | | | | | | | | | | | | | x | x | x | x | x | x | x | x |
| Disease response | | | | | | | | | | | | | | | | x | x | x | x | x | x | x | x |

# 9. ADVERSE EVENTS

## 9.1 REPORTING REQUIRMENTS

The collection and reporting of Adverse Events (AEs) will be in accordance with the Research Governance Framework for Health and Social Care and the requirements of the National Research Ethics Service (NRES). Definitions of different types of AE are listed in Appendix 5. The Investigator should assess the seriousness and causality (relatedness) of all AEs experienced by the patient (this should be documented in the source data) with reference to the protocol.

### 9.1.1 Procedures for Collecting Adverse Events

All medical occurrences which meet the definition of an Serious Adverse Event (SAE) should be reported on an SAE Form and sent to the ArChIMEDEs-Op Study Office. Investigators should report AEs that meet the definition of an SAE (see Appendix 5 for definition).

All toxicities (except mucositis) will be reviewed using the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0, (contained in the Investigator Site File). Any toxicities experienced by the patient but not included in the CTCAE should be graded by a Investigator and be recorded on the SAE Form using a scale of (1) mild, (2) moderate or (3) severe (as defined in Appendix 5). For each sign/symptom, the highest grade observed since the last visit should be recorded. In addition Grade ≥4 acute or late radiation side effects (NCI CTCAE version 4.0) occurring within 5 years of radiotherapy treatment should be subject to reporting on the SAE Form. Defined toxicities will be recorded on the On-Treatment Toxicity Assessment Form, Post-Treatment Toxicity Assessment Form and Late Toxicity Follow-up Form (RTOG and CTCAE).

### 9.1.2 Expected Serious Adverse Events

For the purposes of this protocol anticipated treatment related SAEs of Grade ≤ 3 are not subject to expedited reporting but are recorded in the CRFs. Likewise any abnormal laboratory findings and hospital admissions for symptom control for expected chemotherapy / radiotherapy toxicity do not require reporting on the SAE Form. It is expected that patients receiving chemoradiotherapy for head and neck cancers commonly require admission for symptom control. For the purpose of study, the following are regarded as expected SAEs and should not be reported on an SAE form:

- SAEs that are thought to have occurred as a result of the standard head and neck chemoradiotherapy within 4 weeks of completing treatment. These include CTCAE grade 3 side effects such as blood and lymphatic system disorders (leukopenia, thrombocytopenia and anaemia), mucositis, skin reaction, dysphagia, pain, nausea and vomiting, fever, diarrhoea, weight loss, poor oral intake and tinnitus (chemotherapy related), infection and bone marrow suppression. Patients also often require intravenous hydration, nasogastric (NG) feeding tube or percutaneous endoscopic gastrostomy (PEG) feeding and pain control
- SAEs that are related to a pre-existing condition
- SAEs that are related to symptoms or progression of the patient's cancer

This is not an exclusive list and if there is any doubt whether toxicity is expected or not then an SAE Form should be completed.

### 9.1.3 Monitoring Pregnancies for Potential Serious Adverse Events

It is important to monitor the outcome of pregnancies of patients in order to provide SAE data on congenital anomalies or birth defects.

In the event that a patient or their partner becomes pregnant during the SAE reporting period please complete a Release of Medical Information Form (providing the patient's details) and return to the ArChIMEDEs-Op Study Office as soon as possible. If it is the patient who is pregnant provide outcome data

on a follow-up Release of Medical Information Form. Where the patient's partner is pregnant consent must first be obtained and the patient should be given *a* Release of Medical Information Form to give to their partner. If the partner is happy to provide information on the outcome of their pregnancy they should sign the Release of Medical Information Form. Once consent has been obtained provide details of the outcome of the pregnancy on a follow-up Pregnancy Notification Form. If appropriate also complete an SAE Form as detailed below.

### 9.1.4 Reporting Period

Details of all SAEs (except those listed above) will be documented and reported from the date of commencement of protocol defined treatment until 30 days after the administration of the last treatment. Investigators should report AEs that meet the definition of an SAE within 24 hours of first knowledge of the event.

## 9.2 REPORTING PROCEDURE

### 9.2.1 Site

#### *9.2.1.1 Serious Adverse Events*

For more detailed instructions on SAE reporting refer to the SAE Form Completion Guidelines contained in section 5 of the ISF.

AEs defined as serious and which require reporting as an SAE (excluding events listed in Section 8.1.2 above) should be reported on an SAE Form.

On becoming aware that a patient has experienced an SAE, the Investigator (or delegate) must complete, date and sign an SAE Form. When completing the form, the Investigator will be asked to define the causality and the severity of the AE which should be documented using the CTCAE version 4.0 and CTCAE version 3.0 for mucositis. The form should be faxed together with a SAE Fax Cover Sheet to the ArChIMEDEs-Op Study Office using one of the numbers listed below as soon as possible and no later than 24 hours after first becoming aware of the event:

**To report an SAE, fax the SAE form with an SAE Fax Cover Sheet to:**

**0121 414 8392 or 0121 414 3700**

On receipt the ArChIMEDEs-Op Study Office will allocate each SAE a unique reference number. This number will be transcribed onto the SAE Fax Cover Sheet which will then be faxed back to the site as proof of receipt. If confirmation of receipt is not received within 1 working day please contact the ArChIMEDEs-Op Study Office. The SAE reference number should be quoted on all correspondence and follow-up reports regarding the SAE. The SAE Fax Cover Sheet completed by the ArChIMEDEs-Op Study Office should be filed with the SAE Form in the ISF.

For SAE Forms completed by someone other than the Investigator the Investigator will be required to countersign the original SAE Form to confirm agreement with the causality and severity assessments. The form should then be returned to the ArChIMEDEs-Op Study Office in the post and a copy kept in the ISF.

Investigators should also report SAEs to their own Trust in accordance with local practice.

#### *9.2.1.2 Provision of Follow-up Information*

Patients should be followed up until resolution or stabilisation of the event. Follow-up information should be provided on a new SAE Form (refer to the SAE Form Completion Guidelines for further information).

### 9.2.2 ArChIMEDEs-Op Study Office

On receipt of an SAE Form seriousness and causality will be determined independently by a Clinical Coordinator. An SAE judged by the Investigator or Clinical Coordinator to have a reasonable causal relationship with the study treatment will be regarded as a related SAE. The Clinical Coordinator will also assess all related SAEs for expectedness. If the event is unexpected (i.e. is not defined in the protocol as an expected event) it will be classified as an Unexpected and Related SAE.

### 9.2.3 Reporting to the Research Ethics Committee

#### *9.2.3.1 Unexpected and Related Serious Adverse Events*

The ArChIMEDEs-Op Study Office will report all fatal or life threatening Unexpected and Related SAE to the Research Ethics Committee (REC) within 7 days of receiving initial notification. Any follow-up information will be provided within additional days. Non-fatal or non-life threatening Unexpected and Related SAE will be reported within 15 days.

#### *9.2.3.2 Other Safety Issues Identified During the Course of the Study*

The REC will be notified immediately if a significant safety issue is identified during the course of the study.

#### *9.2.3.3 Investigators*

Details of all Unexpected and Related SAEs and any other safety issue which arises during the course of the study will be reported to Investigators. A copy of any such correspondence should be filed in the ISF.

# 10. DATA HANDLING AND RECORD KEEPING

## 10.1 CASE REPORT FORMS

The Case Report Form will comprise the following forms:

| Form | Summary of data recorded | Schedule for submission |
|---|---|---|
| Eligibility | Confirmation of consent. Confirmation patient meets inclusion and exclusion criteria | As soon as possible after study entry |
| Registration and Study Entry | Patient details (including patient initials, date of birth and hospital number). Confirmation patient meets inclusion and exclusion criteria, and patient details | As soon as possible after study entry |
| Baseline A and Baseline B | Details of patient's medical history, and baseline assessments including details of imaging and tumour grade and size. | As soon as possible after study entry |
| Plan Assessment | Full details of scans and treatment planning | As soon as the form as been completed at the scheduled time point |
| Radiotherapy Treatment | Details of tumour grade and involvement and dose and fraction of radiotherapy delivered | As soon as possible after completion of radiotherapy treatment |
| Concurrent Chemotherapy Treatment | Details of dose and cycles of concurrent chemotherapy delivered | As soon as possible after completion of radiotherapy treatment |
| Induction Chemotherapy Treatment | Details of dose and cycles of induction chemotherapy delivered | As soon as possible after completion of radiotherapy treatment |
| Post Chemotherapy Compliance | Details of treatment compliance and reasons for delayed treatment | As soon as the form as been completed at the scheduled time point |
| Post Radiotherapy Compliance | Details of treatment compliance and reasons for delayed treatment | As soon as the form as been completed at the scheduled time point |
| 3 month response to treatment | Details of study treatment and assessment and response to treatment after completion of chemo-radiotherapy | As soon as the form as been completed at the scheduled time point |
| 6 to 60 month follow-up | Details of study treatment and assessment and response to treatment after completion of chemo-radiotherapy | At 6, 12, 18, 24, 36, 48 and 60 months post-treatment |
| On-Treatment Toxicity | Weekly assessment during radiotherapy. Weekly during the first 6 weeks or until resolution of Grade 3 mucositis | As soon as the form as been completed at the scheduled time point |
| Post-Treatment Toxicity | Weekly assessment until resolution of Grade 3 mucositis | As soon as the form as been completed at the scheduled time point |
| Late Toxicity Follow-up (RTOG and CTCAE) | Toxicity assessment | As soon as the form as been completed at the scheduled time point |
| Serious Adverse Event (SAE) | Patient details, causality, outcome, concomitant medication | Immediately upon discovering that the patient has experienced an |

| | | |
|---|---|---|
| | | SAE |
| Notification of Deviation | Used to notify Study Office of a deviation from the study protocol. Date, type and reason for deviation | Immediately upon discovering a deviation |
| Notification of Withdrawal | Used to notify Study Office of patient withdrawal from the study.<br>Reason for treatment discontinuation, and date study treatment discontinued | Immediately upon patient withdrawal |
| Notification of Recurrence | Date, site and detection of recurrence | Immediately upon recurrence |
| Notification of Death | Date and cause of death | Immediately upon notification of patient's death |
| Release of Medical information | Notification of pregnancy during treatment | Immediately upon notification |

The CRF must be completed, signed/dated and returned to the ArChIMEDEs-Op Study Office by the Investigator or an authorised member of the site research team (as delegated on the Site Signature and Delegation Log) within the timeframe listed above. The exceptions to this are the SAE Form and Withdrawal Form which must be co-signed by the investigator. The completed originals should be sent to the ArChIMEDEs-Op Study Office, with a copy held by the Investigator at site.

Entries on the CRF should be made in ballpoint pen, in blue or black ink, and must be legible. Any errors should be crossed out with a single stroke, the correction inserted and the change initialled and dated. If it is not obvious why a change has been made, an explanation should be written next to the change. Typing correction fluid should not be used.

Data reported on each form should be consistent with the source data or the discrepancies should be explained. If information is not known, this must be clearly indicated on the form. All missing and ambiguous data will be queried. All sections are to be completed before returning to the ArChIMEDEs-Op Study Office.

In all cases it remains the responsibility of the Investigator to ensure that the CRF has been completed correctly and that the data are accurate.

Study forms may be amended by the ArChIMEDEs-Op Study Office, as appropriate, throughout the duration of the study. Whilst this will not constitute a protocol amendment, new versions of the form must be implemented by participating sites immediately on receipt.

## 10.2 ARCHIVING

It is the responsibility of the Investigator to ensure all essential study documentation and source records (e.g. signed Informed Consent Forms, Investigator Site File, patients' hospital notes, copies of CRFs etc) at their site are securely retained for at least 5 years after the end of the study. Do not destroy any documents without prior approval from the CRCTU Document Storage Manager.

# 11. QUALITY MANAGEMENT

ArChIMEDEs-Op study will be coordinated by the Cancer Research UK Clinical Trials Unit at the University of Birmingham according to the current guidelines for Good Clinical Practice (GCP).

## 11.1 ON SITE MONITORING

Monitoring will be carried out as required following a risk assessment and as documented in the ArChIMEDEs-Op Quality Management Plan according to CRCTU policy. On-site monitoring visits may be triggered for example by poor CRF return, poor data quality, low SAE reporting rates, excessive number of patient withdrawals or deviations. If a monitoring visit is required the ArChIMEDEs-Op Study Office will contact the site to arrange a date for the proposed visit and will provide the site with written confirmation. Investigators will allow the ArChIMEDEs-Op study staff access to source documents as requested.

## 11.2 CENTRAL MONITORING

Where a patient has given explicit consent sites are requested to send in copies of signed Informed Consent Forms for in-house review.

Study staff will be in regular contact with the site research team to check on progress and address any queries that they may have. Study staff will check incoming CRFs for compliance with the protocol, data consistency, missing data and timing. Sites will be sent Data Clarification Forms requesting missing data or clarification of inconsistencies or discrepancies.

Sites may be suspended from further recruitment in the event of serious and persistent non-compliance with the protocol and/or GCP, and/or poor recruitment. Any major problems identified during monitoring may be reported to Trial Management Group. This includes reporting serious breaches of GCP and/or the study protocol to the REC.

## 11.3 AUDIT AND INSPECTION

The Investigator will permit study-related monitoring, audits, ethical review, and regulatory inspection(s) at their site, providing direct access to source data/documents.

## 11.4 NOTIFICATION TO SPONSOR

The Sponsor of the Study is responsible for notifying the REC in writing of any serious breach of the protocol relating to the study, within 7 days of becoming aware of that breach. A “serious breach” is defined as a breach which is likely to effect to a significant degree:

- The safety or physical or mental integrity of the subjects of the study; or
- The scientific value of the study

The investigator is therefore requested to notify the ArChIMEDEs-Op Study Office of a suspected study-related serious breach of GCP and/or the study protocol. Where the ArChIMEDEs-Op Study Office is investigating whether or not a serious breach has occurred, the site is also requested to cooperate with the ArChIMEDEs-Op Study Office in providing sufficient information to report the breach to the REC and in undertaking any corrective and/or preventive action.

# 12. STATISTICAL CONSIDERATION

## 12.1 POWER CALCULATIONS

The trial design is a single stage feasibility study of 15 patients.

## 12.2 ANALYSIS OF OUTCOME MEASURES

The primary outcome measure will be reported as the percentage of recruited patients with treatment 'success' together with an associated 95% confidence interval.

Categorical data will be reported descriptively as percentages with 95% confidence intervals. Time to event data will be analysed using the Kaplan-Meier method of estimation and survival estimates presented with 95% confidence intervals.

## 12.3 PLANNED SUB-GROUP ANALYSES

There are no planned sub-group analyses.

## 12.4 PLANNED FINAL ANALYSES

The final analysis of the primary outcome measure will take place as soon as all registered patients had completed treatment and been followed up for 3 months. Other secondary outcomes that could be reported at this time include duration of Grade 3 mucositis, incidence of Grade 4 toxicity and response rate. Longer follow-up would be needed for other secondary outcome measures with final analysis when patients have been followed up for a minimum of 5 years.

## 12.5 EARLY STOPPING RULE

The occurrence of Grade 3 mucositis in 2 patients at 90 days (assessment week 13). ≥ Grade 3 late RT induced complication in more than 2 patients at one year.

## 13. END OF STUDY DEFINITION

The end of study will be the date of the last data capture. The ArChIMEDEs-Op Study Office will notify the REC that the study has ended and a summary of the clinical study report will be provided within 12 months of the end of study.

## 14. STUDY ORGANISATIONAL STRUCTURE

### 14.1 SPONSOR

The ArChIMEDEs-Op study will be sponsored by University Hospitals Birmingham NHS Foundation Trust.

### 14.2 CO-ORDINATING CENTRE

The study is being conducted under the auspices of the CRCTU according to their local procedures.

### 14.3 TRIAL MANAGEMENT GROUP

The Investigator, Co-investigators, Trial Statistician, Senior Trial Manager and Trial Coordinator will form the Trial Management Group (TMG). The TMG will be responsible for the day-to-day conduct of the study. They will be responsible to study set-up, and on-going management of the study, the interpretation of the results and preparation and presentation of relevant publications. The TMG will be responsible for the review of:

- All reports of toxicity and line listings of SAEs
- Partient's withdrawals
- Accrual rates
- Completeness of data
- Efficacy data

### 14.4 FINANCE

This is a clinician-initiated and clinician-led study funded by Queen Elizabeth Hospital Birmingham Charities. No individual per patient payment will be made to the NHS Trust, Investigators or patients.

## 15. ETHICAL CONSIDERATION

The study will be conducted in accordance with the Research Governance Framework for Health and Social Care, the applicable UK Statutory Instruments, (which include the Data Protection Act 1998 and Human Tissue Act 2008*)* and the International Conference on Harmonisation Guidelines for Good Clinical Practice (ICH GCP). The study will be submitted to and approved by the REC prior to circulation.

Before any patients are enrolled into the study, the Investigator is required to obtain local Research and Development (R&D) approval. The site will not be permitted to enrol patients until written confirmation of R&D approval is received by the ArChIMEDEs-Op Study Office.

It is the responsibility of the Investigator to ensure that all subsequent amendments gain the necessary local approval. This does not affect the individual clinicians' responsibility to take immediate action if thought necessary to protect the health and interest of individual patients.

## 16. CONFIDENTIALITY AND DATA PROTECTION

Personal data recorded on all documents will be regarded as strictly confidential and will be handled and stored in accordance with the Data Protection Act 1998. With the patient's consent, their specific patient identifiers e.g. patient initials, date of birth, hospital number will be collected at study entry. Patients will be identified using only their unique RNO, initials, hospital number and date of birth on the CRFs and correspondence between the ArChIMEDEs-Op Study Office and the site. However patients are asked to give permission for the ArChIMEDEs-Op Study Office to be sent copies of their signed Informed Consent Forms which will not be anonymised. This will be used to perform in-house monitoring of the consent process. The Investigator must maintain documents not for submission to the ArChIMEDEs-Op Study Office (e.g. Patient Identification Logs) in strict confidence. In the case of specific issues and/or queries from the regulatory authorities, it will be necessary to have access to the complete study records, provided that patient confidentiality is protected.

The ArChIMEDEs-Op Study Office will maintain the confidentiality of all patient's data and will not disclose information by which patients may be identified to any third party other than those directly involved in the treatment of the patient and organisations for which the patient has given explicit consent for data and tissue transfer (e.g. Laboratory staff at Newcastle-upon-Tyne Hospitals Foundation Trust). Pathology Reports and screening results sent by Pathology Laboratory, Newcastle-upon-Tyne Hospitals Foundation Trust to CRCTU will be identified using only patient's RNO, patient initials, hospital number and date of birth. Representatives of the ArChIMEDEs-Op study team may be required to have access to patient's notes for quality assurance purposes but patients should be reassured that their confidentiality will be respected at all times.

## 17. INSURANCE AND INDEMNITY

The ArChIMEDEs-Op study will be run by CRCTU, University of Birmingham. The University Hospitals Birmingham NHS Foundation Trust will act as the study sponsor. University of Birmingham employees are indemnified by the University insurers for negligent harm caused by the design or co-ordination of the clinical trials they undertake while in the University's employment.

NHS Trust and non-Trust hospitals have a duty to care for patients treated, whether or not the patient is taking part in a clinical trial. Compensation is therefore available via NHS indemnity in the event of clinical negligence having been proven.

The University of Birmingham cannot offer indemnity for non-negligent harm. There are no specific arrangements for compensation made in respect of any SAEs occurring through participation in the study, whether from side effects listed or others yet unforeseen.

## 18. PUBLICATION POLICY

Results of this study will be submitted for publication in a peer reviewed journal. The manuscript will be prepared by the TMG and authorship will be determined by mutual agreement.

Any secondary publications and presentations prepared by Investigators must be reviewed by the TMG. Manuscripts must be submitted to the TMG in a timely fashion and in advance of being submitted for publication, to allow time for review and resolution of any outstanding issues. Authors must acknowledge that the study was performed with the support of University Hospitals Birmingham NHS Foundation Trust and CRCTU.

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## APPENDIX 1: COMMON TOXICITY CRITERIA GRADING

Toxicities will be recorded according to the Common Terminology Criteria for Adverse Events (CTCAE), version 4.0. The full CTCAE document is available on the National Cancer Institute (NCI) website, the following address was correct when this version of the protocol was approved: Mucositis will be graded using NCI CTCAE version 3 which is based on a visible scoring system:

Grade 1: Erythema of the mucosa

Grade 2: Patchy ulceration or pseudomembranes

Grade 3: Confluent ulceration or pseudomembranes; bleeding with minor trauma

Grade 4: Tissue necrosis; significant spontaneous bleeding; life threatening consequences

Grade 5: Death

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

## APPENDIX 2: RTOG SCORING

| Grade | | | | | |
|---|---|---|---|---|---|
| **Toxicity** | **0** | **1** | **2** | **3** | **4** |
| Bone | No change from baseline | Asymptomatic; no growth retardation; reduced bone density | Moderate pain or tenderness; growth retardation; irregular bone sclerosis | Severe pain or tenderness; complete arrest of bone growth; dense bone sclerosis | Necrosis/ spontaneous fracture |
| Oesophagus | No change from baseline | Mild fibrosis; slight difficulty in swallowing solids; no pain on swallowing | Unable to take solid food normally; swallowing semi-solid food; dilatation may be indicated | Severe fibrosis; able to swallow only liquids; may have pain on swallowing; dilation required | Necrosis/ perforation; fistula |
| Joint | No change from baseline | Mild joint stiffness; slight limitation of movement | Moderate stiffness; intermittent or moderate joint pain; moderate limitation of movement | Severe joint stiffness; pain with severe limitation of movement | Necrosis/complete fixation |
| Larynx | No change from baseline | Hoarseness; slight arytenoid edema | Moderate arytenoid edema; chondritis | Severe edema; severe chondritis | Necrosis |
| Mucous membrane | No change from baseline | Slight atrophy and dryness | Moderate atrophy and telangiectasia; little mucus | Marked atrophy with complete dryness; severe telangiectasia | Ulceration |
| Salivary glands | No change from baseline | Slight dryness of mouth; good response on stimulation | Moderate dryness of mouth; poor response on stimulation | Complete dryness of mouth; no response on stimulation | Fibrosis |
| Skin | No change from baseline | Slight atrophy; pigmentation change; some hair loss | Patchy atrophy; moderate telangiectasia; total hair loss | Marked atrophy; gross telangiectasia | Ulceration |
| Spinal cord | No change from baseline | Mild Lhermitte's syndrome | Severe Lhermitte's syndrome | Objective neurological findings at or below cord level treatment | Mono-, para-, quadriplegia |
| Subcutaneous tissue | No change from baseline | light induration (fibrosis) and loss of subcutaneous fat | Moderate fibrosis but asymptomatic; slight field contracture; < 10% linear reduction | Severe induration and loss of subcutaneous tissue; field contracture > 10% linear measurement | Necrosis |
| Radiatio-other (Specify,_____) | None | Mild | Moderate | Severe | Life-threatening or disabling |

## APPENDIX 3: WHO PERFORMANCE SCALES

| Status | Description |
|---|---|
| **0** | Asymptomatic, fully active and able to carry out all pre-disease performance without restriction. |
| **1** | Symptomatic, fully ambulatory but restricted in physically strenuous activity and able to carry out performance of a light or sedentary nature e.g. light housework, office work. |
| **2** | Symptomatic, ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours: in bed less than 50% of day. |
| **3** | Symptomatic, capable of only limited self-care, confined to bed or chair more than 50% of waking hours, but not bed-ridden. |
| **4** | Completely disabled. Cannot undertake any self-care. Totally bed-ridden. |

## APPENDIX 4: TUMOUR STAGING- TNM CLASIFICATION

The TNM Classification of Malignant Tumors (TNM) is a cancer staging system that describes the extent of cancer in a patient's body.

- T describes the size of the tumor and whether it has invaded nearby tissue,
- N describes regional lymph nodes that are involved,
- M describes distant metastasis (spread of cancer from one body part to another).

**T** (a, CIS,(0),1–4): size or direct extent of the primary tumor

**N** (0–3): degree of spread to regional lymph nodes

- N0: tumor cells absent from regional lymph nodes
- N1: regional lymph node metastasis present; (at some sites: tumor spread to closest or small number of regional lymph nodes)
- N2: tumor spread to an extent between N1 and N3 (N2 is not used at all sites)
- N3: tumor spread to more distant or numerous regional lymph nodes (N3 is not used at all sites)

**M** (0/1): presence of metastasis

- M0: no distant metastasis
- M1: metastasis to distant organs (beyond regional lymph nodes)

## APPENDIX 5: DEFINITION OF ADVERSE EVENTS

**Adverse Event**

Any untoward medical occurrence in a patient or clinical trial subject participating in the trial which does not necessarily have a causal relationship with the treatment received.

Comment:

An AE can therefore be any unfavourable and unintended sign (including abnormal laboratory findings), symptom or disease temporally associated with the use of a medicinal product, whether or not related to the medicinal product.

**Related Event**

An event which resulted from the administration of any of the research procedures.

**For the purposes of this protocol anticipated treatment related SAEs of Grade ≤ 3 are not subject to expedited reporting but are recorded in the CRFs. Likewise hospital admissions for symptom control for expected chemotherapy / radiotherapy toxicity do not require reporting on the SAE reporting form.**

**Serious Adverse Event**

An untoward occurrence that:

- Results in death Is life-threatening*
- Requires hospitalisation** or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity
- Consists of a congenital anomaly/ birth defect
- Or is otherwise considered medically significant by the Investigator***

In addition Grade ≥4 acute or late radiation side effects (NCI CTCAE version 4.0) occurring within 5 years of radiotherapy treatment should be subject to reporting on the SAE Form.

Comments:

The term severe is often used to describe the intensity (severity) of a specific event. This is not the same as serious, which is based on patients/event outcome or action criteria.

* Life threatening in the definition of an SAE refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.

**Hospitalisation is defined as an unplanned, formal inpatient admission, even if the hospitalisation is a precautionary measure for continued observation. Thus hospitalisation for protocol treatment (e.g. line insertion), elective procedures (unless brought forward because of worsening symptoms) or for social reasons (e.g. respite care) are not regarded as an SAE.

*** Medical judgment should be exercised in deciding whether an AE is serious in other situations. Important AEs that are not immediately life threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should be considered serious.

**Unexpected and Related Event**

An event which meets the definition of both an Unexpected Event and a Related Event.

**Unexpected Event**

The type of event that is not listed in the protocol as an expected occurrence.

## APPENDIX 6: DECLARATION OF HELSINKI

**WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI (1886 Version)**

**Recommendations guiding physicians in biomedical research involving human subjects**

Adopted by the 18th World Medical Assembly, Helsinki, Finland, June 1964 and amended by the

29th World Medical Assembly, Tokyo, Japan, October 1975, 35th World Medical Assembly, Venice, Italy, October 1983, 41st World Medical Assembly, Hong Kong, September 1989 and the 48th General Assembly, Somerset West, Republic of South Africa, October 1996

**INTRODUCTION**

It is the mission of the physician to safeguard the health of the people. His or her knowledge and conscience are dedicated to the fulfilment of this mission.

The Declaration of Geneva of the World Medical Association binds the physician with the words, "The Health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."

The purpose of biomedical research involving human subjects must be to improve diagnostic, therapeutic and prophylactic procedures and the understanding of the aetiology and pathogenesis of disease.

In current medical practice most diagnostic, therapeutic or prophylactic procedures involve hazards. This applies especially to biomedical research.

Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.

In the field of biomedical research a fundamental distinction must be recognized between medical research in which the aim is essentially diagnostic or therapeutic for a patient, and medical research, the essential object of which is purely scientific and without implying direct diagnostic or therapeutic value to the person subjected to the research.

Special caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.

Because it is essential that the results of laboratory experiments be applied to human beings to further scientific knowledge and to help suffering humanity, the World Medical Association has prepared the following recommendations as a guide to every physician in biomedical research involving human subjects. They should be kept under review in the future. It must be stressed that the standards as drafted are only a guide to physicians all over the world. Physicians are not relieved from criminal, civil and ethical responsibilities under the laws of their own countries.

**I. BASIC PRINCIPLES**

1. Biomedical research involving human subjects must conform to generally accepted scientific principles and should be based on adequately performed laboratory and animal experimentation and on a thorough knowledge of the scientific literature.
2. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol which should be transmitted for consideration, comment and guidance to a specially appointed committee independent of the investigator and the sponsor provided that this independent committee is in conformity with the laws and regulations of the country in which the research experiment is performed.

3. Biomedical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given his or her consent.
4. 4. Biomedical research involving human subjects cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject.
5. Every biomedical research project involving human subjects should be preceded by careful assessment of predictable risks in comparison with foreseable benefits to the subject or to others. Concern for the interests of the subject must always prevail over the interests of science and society.
6. The right of the research subject to safeguard his or her integrity must always be respected. Every precaution should be taken to respect the privacy of the subject and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.
7. Physicians should abstain from engaging in research projects involving human subjects unless they are satisfied that the hazards involved are believed to be predictable. Physicians should cease any investigation if the hazards are found to outweigh the potential benefits.
8. In publication of the results of his or her research, the physician is obliged to preserve the accuracy of the results. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.
9. In any research on human beings, each potential subject must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the study and the discomfort it may entail. He or she should be informed that he or she is at liberty to abstain from participation in the study and that he or she is free to withdraw his or her consent to participation at any time. The physician should then obtain the subject's freely-given informed consent, preferably in writing.
10. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship to him or her or may consent under duress. In that case the informed consent should be obtained by a physician who is not engaged in the investigation and who is completely independent of this official relationship.
11. In case of legal incompetence, informed consent should be obtained from the legal guardian in accordance with national legislation. Where physical or mental incapacity makes it impossible to obtain informed consent, or when the subject is a minor, permission from the responsible relative replaces that of the subject in accordance with national legislation. Whenever the minor child is in fact able to give a consent, the minor's consent must be obtained in addition to the consent of the minor's legal guardian.
12. The research protocol should always contain a statement of the ethical considerations involved and should indicate that the principles enunciated in the present Declaration are complied with.

**II. MEDICAL RESEARCH COMBINED WITH PROFESSIONAL CARE**
**(Clinical Research)'**

1. In the treatment of the sick person, the physician must be free to use a new diagnostic and therapeutic measure, if in his or her judgement it offers hope of saving life, re-establishing health or alleviating suffering.
2. The potential benefits, hazards and discomfort of a new method should be weighed against the advantages of the best current diagnostic and therapeutic methods.
3. In any medical study, every patient - including those of a control group, if any - should be assured of the best proven diagnostic and therapeutic method. This does not exclude the use of inert placebo in studies where no proven diagnostic or therapeutic method exists.
4. The refusal of the patient to participate in a study must never interfere with the physician-patient relationship.
5. If the physician considers it essential not to obtain informed consent, the specific reasons for this proposal should be stated in the experimental protocol for transmission to the independent committee (I, 2).
6. The physician can combine medical research with professional care, the objective being the acquisition of new medical knowledge, only to the extent that medical research is justified by its potential diagnostic or therapeutic value for the patient.

**III. NON-THERAPEUTIC BIOMEDICAL RESEARCH INVOLVING HUMAN SUBJECTS (Non-Clinical Biomedical Research)**

1. In the purely scientific application of medical research carried out on a human being, it is the duty of the physician to remain the protector of the life and health of that person on whom biomedical research is being carried out.
2. The subject should be volunteers - either healthy persons or patients for whom the experimental design is not related to the patient's illness.
3. The investigator or the investigating team should discontinue the research if in his/her or their judgement it may, if continued, be harmful to the individual.
4. In research on man, the interest of science and society should never take precedence over considerations related to the wellbeing of the subject.

## CO-ORDINATING TRIALS OFFICE

**ArChIMEDEs-Op Study Office**
**Cancer Research UK Clinical Trials Unit**
**School of Cancer Sciences**
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## REGISTRATION

**Tel:** **0800 371 969 (Monday to Friday, 9:00am till 5:00pm)**

## SERIOUS ADVERSE EVENT REPORTING

**Fax SAE Forms to:**

**0121 414 8392 or 0121 414 3700**