# PETNECK 2

**PET-CT guided, symptom-based, patient-initiated surveillance versus clinical follow-up in advanced head neck cancer**

*Protocol for Work Streams 3a and 3b*

**Protocol Version 2.0, 10 December 2020**

| | |
|---|---|
| **Sponsor:** | **University of Birmingham** |
| **Funder:** | **National Institute for Health Research (NIHR PGfAR)** |
| **IRAS ID:** | **273316** |
| **Sponsor Number:** | **RG_19-164** |

UNIVERSITY OF BIRMINGHAM

FUNDED BY NIHR | National Institute for Health Research

InHANSE Institute of Head and Neck Studies and Education

## TABLE OF CONTENTS

## PROGRAMME MANAGEMENT GROUP

| Chief Investigators | |
|---|---|
| **Dr Paul Nankivell (Chief Investigator)** | Institute of Head and Neck Studies and Education<br>University of Birmingham<br>Birmingham, B15 2TT<br>0121 414 6547 |
| **Prof Hisham Mehanna (Co-Chief Investigator)** | Institute of Head and Neck Studies and Education<br>University of Birmingham<br>Birmingham, B15 2TT<br>0121 414 6547 |
| **Work Stream 3 lead** | |
| **Dr Jo Brett** | School of Nursing and Midwifery<br>Faculty of Health and Life Sciences<br>Oxford Brookes University<br>Oxford, OX3 0FL<br>01865 482696 |
| **Work Stream 3 research group** | |
| **Professor Colin Greaves** | School of Sport, Exercise & Rehabilitation Sciences<br>University of Birmingham<br>Birmingham, B15 2TT<br>0121 414 8061 |
| **Dr Marcus Jepson** | Bristol Medical School<br>University of Bristol<br>Canynge Hall, Whatley Road<br>Bristol, BS8 2PS<br>0117 331 3930 |
| **Professor Mary Wells** | Nursing Directorate, Education Centre, Second Floor<br>Charing Cross Hospital<br>Fulham Palace Road<br>London, W6 8RF<br>0203 3117422 |
| **Professor Melanie Calvert** | Centre for Patient Reported Outcomes Research<br>Institute of Applied Health Research<br>University of Birmingham<br>Birmingham, B15 2TT<br>0121 414 8595 |
| **Dr Philip Kiely** | University Hospitals Bristol NHS Foundation Trust<br>Marlborough Street<br>Bristol, BS1 3NU<br>0117 923 0000 |
| **Professor Joan Duda** | School of Sport, Exercise and Rehabilitation Sciences<br>University of Birmingham<br>Birmingham, B15 2TT<br>0121 414 2737 |
| **Professor Eila Watson** | Oxford Institute of Nursing, Midwifery and Allied Health Research<br>Faculty of Health and Life Sciences<br>Oxford Brookes University<br>Oxford, OX3 0FL<br>01865 482665 |

| Resource development | |
|---|---|
| **Dr Chris Coulson** | Somerset House<br>37 Temple Street<br>Birmingham, B2 5DP |
| **Mr Simon Pargeter** | Somerset House<br>37 Temple Street<br>Birmingham, B2 5DP |
| **Patient and public representatives** | |
| **Mr Denis Secher** | Institute of Head and Neck Studies and Education<br>University of Birmingham<br>Birmingham, B15 2TT |
| **Mrs Pat Rhodes** | Institute of Head and Neck Studies and Education<br>University of Birmingham<br>Birmingham, B15 2TT |
| **Statistical Lead** | |
| **Mr Piers Gaunt** | CRCTU, Institute of Cancer and Genomic Sciences,<br>University of Birmingham<br>Birmingham, B15 2TT<br>0121 414 3410 |
| **PETNECK 2 Programme Manager** | |
| **Saloni Mittal** | Institute of Head and Neck Studies and Education,<br>University of Birmingham<br>Birmingham, B15 2TT |
| **Contact Details** | |
| **PETNECK 2 Trial Office** | Institute of Head and Neck Studies and Education,<br>University of Birmingham<br>Birmingham, B15 2TT<br>0121 414 6547 |
| **Sponsor** | University of Birmingham<br>Research Support Group<br>Aston Webb Building, Room 119<br>Edgbaston, Birmingham, B15 2TT<br>researchgovernance@contacts.bham.ac.uk |

## SIGNATURE PAGE

**PETNECK 2** Protocol (Work Stream 3) Version 2.0, 10 December 2020

**This protocol has been approved by:**

| | | | |
|---|---|---|---|
| **Name:** | Dr Paul Nankivell | **Trial Role:** | Chief Investigator |
| **Signature:** |  | **Date:** | 10 December 2020 |

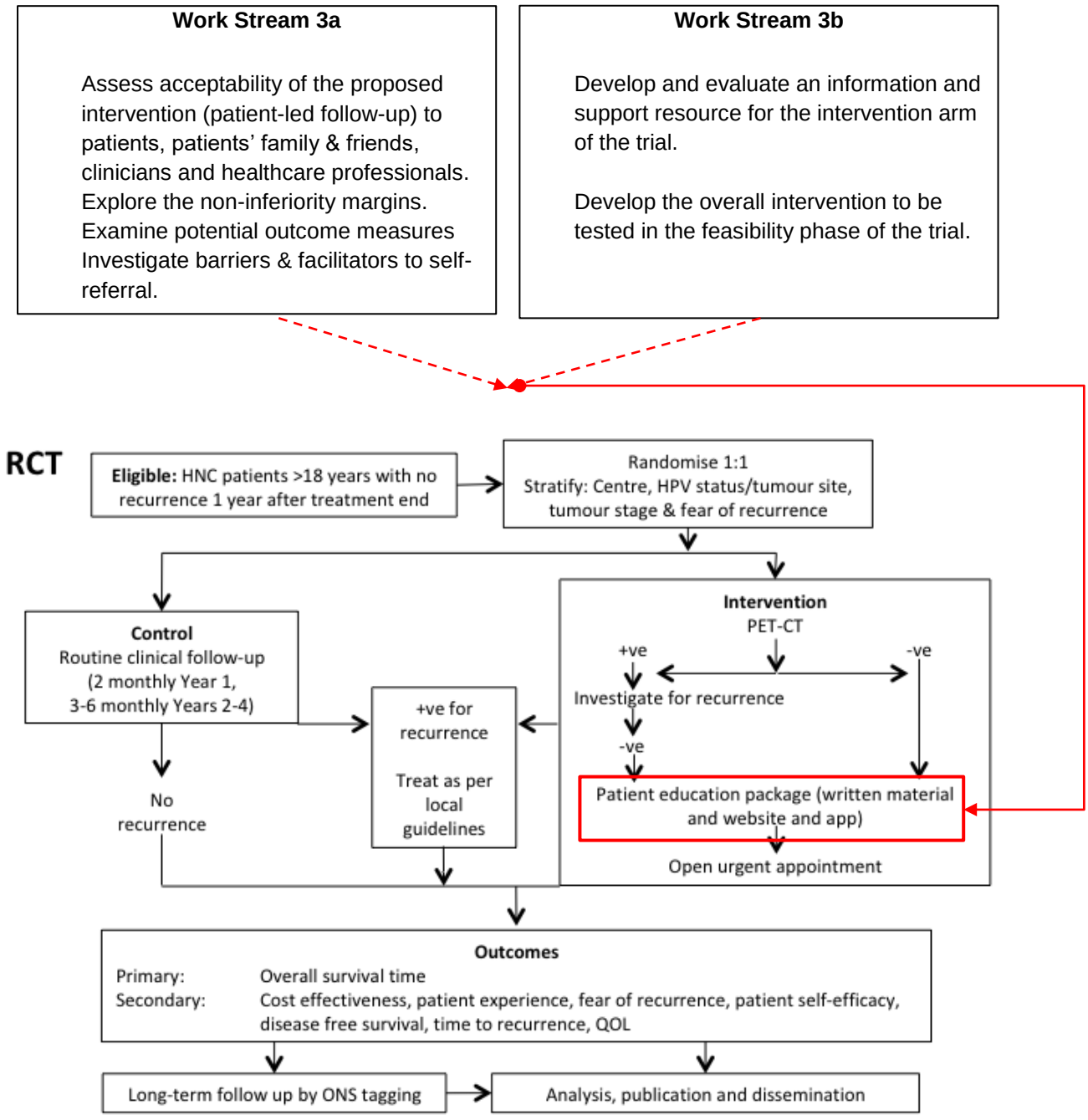
Sponsor statement:
Where the University of Birmingham takes on the sponsor role for protocol development oversight, the signing of the IRAS form by the sponsor will serve as confirmation of approval of this protocol.

## STUDY SUMMARY – WORK STREAM 3

| | |
|---|---|
| **Full Title:** | PET-CT guided, symptom-based, patient-initiated surveillance versus clinical follow-up in advanced head neck cancer (Work Stream 3) |
| **Short title:** | PETNECK 2 |
| **Study design:** | Mixed methods study |
| **Study participants:** | Patients who have been treated for head and neck cancer, patients' family and friends, clinicians, associated health professionals and health care managers associated with head and neck cancer care |
| **Planned study period:** | April 2020 – March 2023 |
| **Research Aim:** | To develop a patient-centred, evidence-based and theoretically informed complex intervention and information and support resource for PETCT-guided, patient-initiated follow-up for head and neck cancer. |

## SCHEMA

This protocol describes work streams 3a and 3b of a larger programme. These work streams are critical in developing the intervention for the planned randomised controlled trial – as depicted below:



## WORKSTREAM 3A SUMMARY

*Design*

This will be a qualitative study, with one-to-one interviews and focus groups. Experienced qualitative researchers will perform semi-structured individual patient interviews (in person or remotely depending on patient preference). In addition, focus groups interviews will be held with head and neck cancer clinicians (surgeons and oncologists) and Allied Health Professionals (AHPs).

*Outcomes measures*

This work stream will:

i) Qualitatively assess the acceptability of the proposed intervention (patient-initiated follow-up) and comparator (routine scheduled clinical follow-up) to patients, patients' family and friends, clinicians, AHPs and healthcare managers.

ii) Qualitatively assess the acceptability to patients of being randomized into a clinical trial with those comparators.

iii) Explore the relevance and suitability of potential outcome measures and the extent to which any differences in outcome between the groups is acceptable. This will inform setting the non-inferiority margins for the main trial. In addition, the barriers and facilitators to self-referral will be explored.

*Eligibility criteria*

Inclusion:

i) Patients who have been treated for head and neck cancer (up to 5 years post treatment) and their family/friends, if patients wish them to be included

ii) A range of stakeholders, including doctors, nurses, AHPs, service managers and/or commissioners

Exclusion:

i) Patients with recurrent or metastatic disease

ii) Patients undergoing treatment for other cancers

iii) Patients lacking capacity to give informed consent

iv) Patients under 18 years old

*Sample size*

Up to 60 patients/family and friends, and up to 60 head and neck healthcare staff and stakeholders.

*Duration*

36 months

## WORKSTREAM 3B SUMMARY

*Design*

i) Review of existing relevant educational and support resources provided by the NHS and UK cancer charities for HNC patients
ii) Workshop 1 – 15-20 patients previously treated for head and neck cancer within 5 years (+/- patients' family and friends)
iii) Survey questionnaire
iv) Workshop 2 – 15-20 patients previously treated for head and neck cancer within 5 years (+/- patients' family and friends)
v) Workshop 3 – 15-20 patients previously treated for head and neck cancer within 5 years (+/- patients' family and friends)
vi) Workshop 4 – 15-20 Allied Health Professionals

*Outcomes measures*

This work stream will:
i) Develop and evaluate an information and support (I&S) resource for the intervention arm of the study
ii) Develop the overall intervention to be tested in the feasibility phase of the trial
iii) Develop and evaluate a training package for practioners delivering the I&S resource

*Eligibility criteria*

Inclusion:
i) Patients who have been treated for head and neck cancer (up to 5 years post treatment) and their family/friends, if patients wish them to be included
ii) A range of stakeholders, including doctors, nurses, AHPs, service managers and/or commissioners involved in the care of head and neck cancer patients

Exclusion:
i) Patients with recurrent or metastatic disease
ii) Patients undergoing treatment for other cancers
iii) Patients lacking capacity to give informed consent
iv) Patients under 18 years old

*Sample size*

Approximately 15-20 patients in each workshop, up to 455 patients in the survey and approximately 20 head and neck healthcare staff.

*Duration*

36 months

# BACKGROUND AND RATIONALE

Head and neck cancer (HNC) is the sixth commonest cancer worldwide, with 640,000 cases diagnosed annually(1).There are 12,000 new cases diagnosed and >4000 deaths annually in the United Kingdom(2). Because of their anatomical location, both the tumours and their treatments result in significant morbidity, including problems with speech and voice, swallowing, pain and disfigurement. Consequently, it has one of the highest disease burdens of any cancer type(3).

Approximately 40% of patients (range 20-57%) treated for HNC most commonly develop cancer recurrence at the primary site or the draining lymph nodes(4). The majority occur in the first two years after treatment (62% in first year, 82% within two years)(5-7). Rates of distant metastases are reported to be between 10-20%(8,9). Despite significant morbidity, salvage surgery provides the best opportunity for long-term survival in patients with recurrent HNC. Crucially however, this is only possible if the recurrent disease is amenable to resection, which is more likely to be the case with early detection(10,11).

Therefore, there is a consensus amongst current treatment guidelines worldwide on the need for routine follow-up, with the principal aim being to detect cancer recurrence and/or distant metastases at the earliest stage possible. There is slight variation between guidelines in the interval of routine follow-up recommended (often varying by 1-2 months only), and the necessity and type of regular imaging (Chest X-ray or CT-scan). The most recent UK national head and neck cancer guidelines recommend that patients undergo clinical follow-up every 2 months for the first 2 years after treatment, and then every 3-6 months for the next 3 years(12). Regular follow-up with clinical examination for a minimum of 5 years following treatment end is also recommended by the American (NCCN), Dutch (DHNS), and Swiss (SSORRL) and European (ECHNO) guidelines (table 1). In a survey of UK practice, 91% of clinicians follow patients up regularly for a minimum of 5 years, with a significant proportion (35%) continuing follow-up for 10 years or longer(13).

| Published guidelines | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 | >Year 5 |
|---|---|---|---|---|---|---|
| UK | 1-2 months | 1-2 months | 3-6 months | 3-6 months | 3-6 months | 12 months |
| NCCN | 1-3 months | 2-4 months | 4-6 months | 4-6 months | 4-6 months | 6-12 months |
| DHNS | 2 months | 3 months | 4 months | 6 months | 6 months | Stop |
| SSORL | 1-3 months | 1-3 months | 4-6 months | 4-6 months | 4-6 months | Stop |
| ECHNO | Not stated | Not stated | Not stated | Not stated | Not stated | Not stated |

Table 1: Follow-up schedule guidelines from different national societies

## 1.1 Justification for research programme

### 1.1.1. Lack of evidence for current follow-up strategy

**Routine clinical follow-up protocols for cancer surveillance, whilst widely accepted, lack a robust evidence-base. They may not be the most effective or cost-effective method of early cancer recurrence detection.**

Whilst being the international standard, current strategies for HNC surveillance lack a robust evidence base and are inefficient. The rate of detection of a cancer recurrence using routine clinical surveillance is low – especially in asymptomatic patients. One study of 1039 consultations identified suspicion of recurrence in only 10% of routine visits(14). In this cohort, suspicion of

cancer recurrence was reported in 0.3% of *asymptomatic* patients seen routinely. Yet, in those patients requesting an appointment to report a new symptom, the rate of suspicion of recurrence rose to 58%, with a negative predictive value of 99.6%(14). In another prospective study of 619 asymptomatic patients attending for routine follow-up, only one recurrence was detected in every 99 routine consultations(6). In a retrospective patient record review, only 12% of patients with detected recurrence were asymptomatic(15).

In addition, the current clinical surveillance strategy detects many recurrences at an advanced stage. In a study of 4839 patients with recurrent HNC, >60% presented at an advanced stage (stage III/IV disease). Advanced stage on recurrence was statistically significantly associated with risk of death on multivariate analysis (HR 1.24, 95%CI 1.20–1.29, p<.0001)(16). In another study, only half of patients with recurrence (51%) were able to be offered salvage treatment, reflecting the advanced stage of disease at the time of recurrence detection(15). In another study, only 27% of patients with detected recurrence were suitable to receive salvage surgery(17).

### 1.1.2. Patient desire for better follow-up strategies

**Follow-up for cancer surveillance is important to patients, who are calling for better methods of cancer recurrence detection. A patient-initiated system may be more responsive to patients' needs.**

Patients are calling for more flexible, patient-centred follow-up(18). 84% of HNC patients in one study felt that current follow-up regimes were too frequent, and 73% favoured intensive follow-up in the first year only, with less intensive, symptom-based appointments thereafter(19). The Alberta Cancer Foundation, supported by the James Lind Alliance (JLA) in the UK, brought together patients, clinicians and researchers in 2017 to jointly determine the most important uncertainties in HNC management. *'How often and for how long should patients be monitored for local recurrence of cancer, and what is the role and effectiveness of annual screenings?'* were key priorities(89).

More recently a similar research priority-setting exercise involving 3500 survivors of all cancer types was undertaken by the National Cancer Research Institute(20). Two of the top research priorities identified by this exercise align closely with our programme of work: *'What is the optimal follow-up approach to detect whether a cancer has come back?'* and '*What are the best ways to cope with the fear and anxiety about cancer returning?'*

### 1.1.3. Lack of data on alternative strategies

**There are few data on alternative strategies of cancer follow-up.**

A recent systematic review of eight studies (n=1927 individuals with breast cancer, inflammatory bowel disease and rheumatoid arthritis) showed that patient-initiated follow-up models were associated with similar clinical outcomes to routine follow-up, but demonstrated significantly better satisfaction, and resource savings(21,22). In HNC, there is limited, poor quality, retrospective and conflicting evidence regarding the relative efficacy of the current strategy of routine follow-up versus symptom-driven self-referral strategies. Of the six studies that we identified in a literature review, four showed no difference in overall survival between routine follow-up and self-referral for HNC patients(23-26). One study showed that all recurrences were identified by self-referral, with no recurrences in asymptomatic patients seen on routine follow-up(27). Conversely, another study of 428 patients showed better survival in the patients who underwent routine follow-up(28). In addition, an ethnographic study showed that barriers to implementing patient-initiated follow-up models do exist and that working with clinicians in local contexts is important for successful implementation(29).

As a result of these significant deficits in the evidence base, clinicians are reluctant to change from the current strategy, as it remains the recommendation of expert panels with no high quality data supporting alternative strategies. *High quality evidence in the form of a prospective trial will be required to change clinical practic*e.

### 1.1.4. Fear of cancer recurrence

**Fear of cancer recurrence is a significant ongoing burden for HNC patients, with significant impact on quality of life. It is not clear whether routine follow-up appointments exacerbate or relieve this.**

On completion of treatment, many patients experience concern that their cancer may return or progress(30,31). This is termed fear of cancer recurrence (FCR) and has a major impact on patients overall quality of life(32,33). FCR occurs along a spectrum, with around half of all cancer survivors experiencing moderate to severe levels of FCR(30,34). For a smaller number, the experience may be so severe as to become debilitating(35).

Despite FCR being well documented in HNC patients(31,33,36,37), there are no studies that have examined the effect of different follow-up regimens on their FCR. Qualitative studies have demonstrated FCR being triggered by forthcoming medical appointments for other conditions(38). As follow-up appointments involve clinical examination or even referral for further tests, FCR may in fact be exacerbated and not improved by this process(39). These increased anxieties around the time of follow-up appointments may be further worsened by a reluctance of patients to discuss these feelings with HNC clinicians(40).

Conversely, there is evidence from a different cancer type suggesting that FCR is lower in patients who are routinely followed up. This recent randomised trial of patient-initiated follow-up for 156 women with early stage endometrial cancer found that the women in the intervention group had fewer examinations compared with the control group (0 vs. 2 median visits, $P < 0.01$), with 58% of their appointments scheduled as a result of symptoms(41). However, FCR decreased significantly more in the control group, compared to the patient-initiated follow-up group (difference −5.9, 95% CI −10.9 to −0.9 from baseline to 10 months of follow-up). Therefore, there remains controversy regarding the effect of routine versus patient-driven surveillance on FCR.

### 1.1.5. Pressure on healthcare resources

**Changing epidemiology of HNC with the exponential rise of HPV+ve HNC, in combination with its higher survival rate and low distant metastasis rates, is leading to a rapidly-enlarging cohort of cancer survivors requiring follow-up, placing significant pressure on finite NHS resources.**

In the last 20 years, there has been a dramatic and exponential rise in the incidence of oropharyngeal squamous cell carcinoma. This increase is driven by Human papillomavirus (HPV) infection and is particularly significant in western countries(42,43). The incidence of HPV associated oropharyngeal cancer (HPV+OPC) in the UK doubled between 1995-2005, then doubled again between 2005-2010(44), with 2977 new cases diagnosed in the UK in 2016. This continued rise will represent a 239% increase in overall oropharyngeal cancer incidence between 2011 and 2025, such that the US Centre for Disease Control recently reported that HPV+OPC has overtaken cervical cancer in the United States(45). This has driven an overall increase of 24% in age-standardised incidence rates of HNC over the last decade in the UK(2).

Importantly, HPV+OPC affects younger patients and has a significantly better prognosis than HNC caused by traditional risk factors of tobacco and alcohol. This has led to a rapidly enlarging cohort of HNC survivors, in turn placing significant pressure on NHS services. In a study from 3

major UK head and neck cancer centres, OPC accounted for more than one-third of their total HNC costs, with costs for this subset doubling over a 4 year period (£17.21 million to £30.32 million)(46).

### 1.2. Proposed Solution

We have previously demonstrated in the HTA-funded PET-NECK trial that a PETCT scan at 3-months post chemoradiotherapy avoided a routine neck dissection operation to remove residual nodal disease in HNC (the previous standard of care) in >80% of patients, with a reduction in harm, and saving of £1415 per patient to the NHS(47). Within two years of its publication, this has become the standard of care in most countries around the world. We now wish to build on the success of the first PET-NECK trial to develop and test the efficacy and cost-effectiveness of a better paradigm for post-treatment surveillance for patients with HNC.

The current standard of care for follow-up of patients with HNC in the UK is clinical surveillance following the schedule outlined in Table 1. If patients have received radiotherapy as primary treatment then they will undergo a form of imaging at 3 months post treatment to assess their response to treatment. After this, all patients will follow close surveillance with clinical examination, and additional imaging only undertaken if there are concerns about recurrence.

In PETNECK 2, we propose patients in the experimental arm of the trial would receive an additional PETCT-scan 1-year after completion of treatment (this is the point of entry to the trial) and instead of regular scheduled follow-up appointments, would then be in control of when they return for follow-up visits (patient-initiated follow-up). We hypothesise that the additional PETCT scan at entry to the trial (at 12 months post treatment) will identify some patients with asymptomatic recurrence, but importantly will also identify those at very low risk of future recurrence. These low risk patients would then receive a face-to-face information and support education session (co-designed by patients who have undergone HNC treatment) delivered by a clinical nurse specialist or allied health professional, who would explore with them any potential barriers to a patient-initiated follow-up system. This session would also aim to educate and empower patients by giving them information on how to monitor their symptoms, understand which ‘red-flag’ symptoms could indicate a recurrence, and how to arrange an urgent follow-up appointment (within two weeks), if they develop such symptoms.

An information and support resource covering red-flag symptoms for head and neck cancer, available resources on the management of the side effects of treatment, and peer-to-peer services that offer support during the care pathway, will be provided in written and electronic (website and app) formats, and would serve as an ongoing resource for patients. Patients will also receive training on how to monitor their symptoms using a personal diary.

### 1.3. PETNECK 2 programme aims and objectives

**Overall programme research question:** Does PETCT-guided, patient-initiated, symptom-based follow-up result in similar overall survival and better cost-effectiveness compared to current post-treatment routine surveillance for HNC patients?

**Overall programme aim:** To assess the efficacy and cost-effectiveness of an alternative active surveillance strategy (using PETCT-guided, patient-initiated, symptom-based follow-up), compared to the current standard of care routine regular clinical follow-up.

**Specific objectives of this study proposal (WS3):**

1) Develop a complex intervention for PETCT-guided, patient-initiated, symptom-based follow-up that is acceptable to patients and clinicians, by: a) Evaluating the acceptability of the proposed intervention to both patients and clinicians, including assessing enablers to and potential barriers to patient-initiated follow-up and b) Guided by evaluation of patients' needs and in collaboration with patients, develop a patient information and support resource delivered in multiple formats, ensuring appropriate, robust and reproducible delivery. The resource will focus on when and how to initiate a request for a follow-up consultation, contact details of the patients' primary healthcare worker, and proposed peer support services.

2) Ensure the patient voice is strongly represented and embedded within the programme's decision-making and conduct to ensure relevance of outcomes to patients and carers, and faster pathways to impact.

It is currently unclear what the optimal intervention is to support patients that would not be undergoing routine clinical follow-up. The work required to investigate how this would be best achieved, what information to include, and how to deliver it in an autonomously motivating way to patients and their family/friends, is critical to being able to design a robust clinical study comparing this new follow-up strategy to current standard of care (routine follow-up).

**This represents Work Streams 3a and 3b of the whole PETNECK 2 programme, and is fundamental in achieving a high-quality, robust and patient-centered intervention to compare to standard of care. This will then be tested in a feasibility, and then a randomized controlled trial, for which separate ethical approval will be sought.**

## 1.4. Work Stream 3a

### 1.4.1. Specific objectives

This work stream will:

i) Assess the acceptability of the proposed intervention (patient-initiated follow-up) and comparator (routine scheduled clinical follow-up) to patients, their family/friends, clinicians and healthcare professionals.

ii) Assess the acceptability to patients of being randomized into a clinical trial with those comparators.

iii) Explore the relevance and suitability of potential outcome measures and the extent to which any differences in outcome between the groups is acceptable. This will inform setting the non-inferiority margins for the main trial. In addition, the barriers and facilitators to self-referral will be explored.

### 1.4.2. Underpinning theory

The QuinteT Recruitment Intervention (QRI) methodology(48) has been developed by members of the group, to qualitatively help understand potential challenges in the design or conduct of an RCT and analyse barriers to recruitment to clinical trials, and to then institute interventions to address these barriers and improve recruitment. The QRI has developed a well established topic guide that is used to guide the qualitative interviews/focus groups with patients and stakeholders and aims to consistently cover topics aligned with the objectives(49). The QRI has been applied successfully to over 40 clinical trials.

### 1.4.3. Methods

Semi-structured interviews by an experienced qualitative researcher will be conducted with:

i) Patients who have been treated for head and neck cancer (up to 5 years post treatment) and their family/friends, if patients wish them to be included.
ii) A range of stakeholders, including doctors, nurses, AHPs, service managers and/or commissioners involved in the care of head and neck cancer patients.

Interviews with patients: Given the potential sensitivity and complexity of the discussions, we intend to undertake individual patient interviews. Interviews will be undertaken either face-to-face, by telephone or videocall, or by email (for patients who cannot speak) according to each respondent's preference – although to minimise costs and potential burden on patients, telephone or videocall or email interviews will be the preferred mode of data collection. If patients would like a family member or friend to be included, they will also be offered the opportunity to be interviewed. This may be concurrently or in a separate interview, depending on the wishes of the patient.

Patient interviews will explore the acceptability of the proposed intervention, the feasibility of delivering the intervention, any barriers and perceived benefits of the intervention, what is considered an acceptable trade-off for survival to inform the inferiority margin of the RCT, and terminology that may help support their understanding of the RCT design.

Interviews will also consider patients' perceived susceptibility and seriousness of recurrence of H&N cancer, their cues to action, self-efficacy and information on other participant modifiable variables, to assess potential barriers to and enablers of self-referral and patient-initiated follow-up, and what support patients feel would be appropriate to support patient-initiated symptom-detection and requests for follow-up if/when symptoms are detected. This information will be used to inform the development of the information and support (I&S) resource (WS3b). If a patient becomes tired during an interview they will be offered a break or if necessary can reconvene at a time convenient to them. If they are affected in any way by the discussions from the interview, support will be provided from the research team.

The indicative topic guide will undergo iterative amendments according to the findings of the interviews.

Focus groups with stakeholders: We will co-ordinate focus group interviews with clinical stakeholders, including head and neck cancer specialists, nurses, allied health professionals, healthcare managers and/or service commissioners. An adapted version of a well-established QRI topic guide will be utilised, that will seek to elicit clinician/nurse/AHPs acceptability of the proposed intervention and of the RCT design, their preferences, margins of equipoise, and any potential organisational barriers and ways of overcoming them. Views on content and format of the I&S resource will also be explored. The focus groups will be grouped by professions although mixed profession focus groups may also be organized.

### 1.4.4. Populations and sampling

A purposive sampling strategy will be applied to recruit patients, clinicians, nurses and AHPs, with a target number of approximately 40 patient interviews

Patients will be recruited via clinics at participating NHS hospital trusts, and supplemented through existing HNC support groups (e.g. Heads2gether), patient advocacy groups (e.g. National Association of Laryngectomee Clubs, Mouth Cancer Foundation, Throat Cancer Foundation) and the National Cancer Research Institute's Consumer Group. The maximum variation sample method will be applied according to tumour groups, treatments received (surgery versus non-surgery), age, gender and educational level.

A multidisciplinary sample of up to 60 doctors, nurses and AHPs from across the UK will be recruited to the focus groups through personal contacts, the British Association of Head & Neck Oncologists (BAHNO) and the British Association of Head and Neck Oncology Nurses (BAHNON), the multidisciplinary professional bodies representing HNC clinicians, clinical nurse specialists, and allied health professionals, including speech and language therapists and dietitians.

### 1.4.5. Analysis

Interviews with patients and clinician/AHP focus groups will be audio recorded, transcribed and interpreted using inductive thematic analysis of all textual data(50). The patient interviews and clinician/AHP focus groups will be rapidly and contemporaneously analysed (concurrently with data collection), and the findings used to inform WS3b below.

## 1.5. Work Stream 3b

### 1.5.1. Specific objectives

This work stream has three key objectives:
1) Develop and evaluate an information and support (I&S) resource for the intervention arm of the study
2) Develop the overall intervention to be tested in the feasibility phase of the trial
3) Develop and evaluate a training package for practitioners delivering the I&S resource

### 1.5.2. Underpinning theory

The intervention, including the I&S resource, will be evidence-based, theoretically informed and patient-centred in line with the Medical Research Council (MRC) framework for complex interventions(51). The development process will draw heavily on robust patient contributions by the Patient Advisory Group, the interdisciplinary expertise of the co-applicants and collaborators and, importantly, the data collected from patient and service provider interviews in WS3a.

The COM-B model and Behaviour Change Wheel will be used to develop a clear specification of the target behaviours, identify key views and beliefs as well as environmental factors influencing the target behaviours and identify intervention techniques to modify these perceptions and environmental determinants. While it is difficult to pre-empt the detail about the content or specific behavioural approaches that might be adopted in the I&S resource and initial patient counselling session, we can provide a few examples of how the process might work. Essentially it is a process of identifying key influences on behaviour and matching these to the behaviour change techniques that are most likely to be accepted by participants and to be effective. For instance, we know from existing evidence that there are a number of barriers for patients to identifying, legitimising and sharing information about cancer symptoms with clinicians. This can be due to (the underlying processes of): a) simple misconceptions or lack of information; b) low quality motivation to take action for other reasons (e.g. other social priorities /busy lives, low self-esteem or loss of self, low self-efficacy about /lack of resources for managing a possible recurrence of cancer); c) underlying anxiety leading to symptom minimisation (a more psychologically driven denial response, or physical limitations e.g. speech and communication difficulties); d) perceptions of the significance of symptoms, particularly in relation to late effects of treatment or co-morbidities; or e) communication or environmental barriers to disclosing information within a busy clinic. If these barriers are confirmed in the preparatory work including WS3a, we would generate a list of candidate behaviour change techniques and strategies to address these barriers. This may, for instance, include: a) providing information to address misconceptions, or demonstration of/providing instruction on a suitable procedure for self-checking /assessing the importance of symptoms; b) using motivational interviewing or other patient-centred counselling techniques to explore perceptions regarding key symptoms and taking action and identifying and overcoming individual barriers to recognizing and raising them; c) using psychological counselling techniques (and possibly a brief screening tool) to identify and address significant anxiety that is preventing engagement (with referral to a specialist for high /clinical levels of anxiety); Providing social support / encouragement. These candidate techniques will be presented to and discussed with our stakeholder groups to identify the ones that are most likely to be acceptable to / engaged with by patients and to be feasible for delivery by provider staff (e.g. they may or may not be comfortable addressing psychological issues / anxiety). We will also consult the evidence base where possible, if there is a choice of techniques to identify techniques that are most likely to be successful in this population (although in practice, that is more likely to depend on the individual / the context of their particular life, so providing a choice of options and allowing individual tailoring is often the preferred strategy).

Via the development and delivery of the intervention, we aim to promote patients' autonomous motivation (personal volition) to engage in the targeted behaviours. The over-arching conceptual framework, which will guide the delivery of the identified techniques, is Self Determination Theory (SDT). This theory holds that autonomous motivation for behavioural engagement will be supported if patients' sense of autonomy,

competence (efficacy) and relatedness are supported. Via the application of the COM-B and Behavioural Change Wheel, we will ascertain the enablers and facilitators of the behaviours in the patients' views. Their input will be solicited and choice will be provided when deciding which techniques will be employed to address the identified enablers and facilitators. Patients' perceptions regarding their confidence to change their behaviours will be determined and they will be asked to suggest strategies to enhance this confidence and identify factors that diminish confidence. Exchanges with the health professional will be conducted in a caring, respectful as well as autonomy supportive manner.

### 1.5.3. Methods

At the start of WS3b, we will undertake a review of existing relevant intervention and support resources provided by the NHS and UK cancer charities for HNC patients, which will further inform the I&S package. The development of the intervention and the I&S resource will follow an iterative process, and will also be informed by: the results of the comprehensive systematic review on HNC patient information needs conducted by NICE(50); the systematic review on efficacy, barriers and facilitators for symptom-based, patient initiated presentation (undertaken in an earlier work stream in the programme - WS2); and by patient and other stakeholder views elicited as part of the patient interviews and focus groups with health professionals conducted in WS3a.

As part of the interviews with patients in WS3a, data will be collected regarding HNC recurrence and potential barriers and facilitators to patient-initiated self-referral. As part of the HNC workshops, data will be collected regarding the preferred content and format of the I&S resource. This data will inform the intervention, including the consultation and I&S resource, on how to overcome perceptual and practical barriers to patient initiated follow-up.

The synthesis of the data from the systematic reviews (WS2), interviews (WS3a), and the review of existing patient information (WS3b) will be conducted using a narrative review method in four stages:

- Developing a preliminary synthesis of findings
- Exploring relationships in the data
- Developing a theory of how the intervention would work, why and for whom
- Assessing the robustness of the synthesis

Summary themes and potential content from the data above will then be presented by researchers at patient co-design workshop 1, which will include approximately 15-20 HNC patients up to five years post treatment. Sampling of patients is detailed below.

The methods for this workshop will follow the Health Service co-design tool kit(68), with groups to brainstorm ideas and engage and stimulate creativity among the stakeholders taking part. Group discussion and informal consensus on content will be reached within the small groups, which will then be fed back to the wider workshop group. This feedback and further discussion around this will be digitally recorded and transcribed(60). The transcripts from workshop 1 will be rapidly analysed by researchers (with input from the Patient Advisory Group), using inductive thematic analysis of all textual data, to inform a prototype of the I&S resource developed.

To further inform the I&S resource we will undertake a survey to identify the most common barriers to and enablers of our target behaviours, building on the barriers/enablers identified in our interviews and focus groups. The survey instrument will be sent to patients with HNC and patients' family and friends (n= up to 455) accessed through clinics, charities and support groups, with an estimated 30% response rate, giving a target of 151 responses. Additional "intervention scaffolding" questions(52) may be included to identify patient preferences with regard to formative intervention options (e.g. frequency of contact, mode of intervention, alternatives to online delivery (if needed) and other adaptations) that might be needed for

different population sub-groups (e.g. people with dyslexia or learning disabilities). The exact content cannot be specified at this stage, as it will emerge from the data collected earlier in WS3a and WS3b. However, we will use the "Behavioural Diagnosis Questionnaire" (53) as a template. A questionnaire with indicative examples of the type of information that might be included is provided. However, it must be noted (as with the interview and focus group topic guides) that the content may need to be adapted as the intervention development process evolves. *A finalised version of the survey questionnaire will be sent to the ethics committee as an amendment prior to distribution.*

The survey is designed to elicit barriers to/enablers of the targeted behaviours relating to: Capability (e.g. knowledge; ability to accurately detect symptoms), Opportunity (e.g. remembering to monitor symptoms; clear channels of communication for reporting symptoms) and Motivation (e.g. understanding the benefits of early intervention /the risks of delay; belief in treatment efficacy; fear; consideration of family /others; the reasons for engaging in the targeted behaviour(s)). While the findings from the survey will help inform the I&S resource, its development is not contingent on achieving the target response.

The prototype I&S resource will be developed according to guidance from the TIDieR checklist(52). All information will follow the NHS England Information Standard (NHS England). Readability of the draft resource will be determined using the Flesch Reading Ease score(54), Flesch- Kincaid Grade Level(55) and Simplified Measure of Gobbledygook (SMOG) grade(56).

We will then convene a meeting of the Programme Management Group, the Patient Advisory Group and a multi-disciplinary Clinical Advisory Group (including clinicians, nurses and health managers) to agree the prototype intervention package and I&S – based on the data obtained from workshop 1.

A hard copy booklet will then be produced. Its content and evidence will also form the basis of the web-based applications, which will be developed by endoscope-i (who are CQC and cyber-essential registered). The electronic I&S resource will be developed as a phone application (app) using iOS/Android operating systems and as a website using desktop operating systems for maximum end user accessibility. The application will consist of a clean, easy-to-use user interface with appropriate accessibility options for those with disabilities. The full I&S package will be contained within it, and remote update of content will be available. It will include inbuilt functionality to allow patients to record and review their own symptoms and quality of life history (symptom diary). At their own discretion, patients may decide to discuss these data directly with their clinical team during consultations.

Consistent with best practice(57), an iterative process will be used to elicit user (patient and health professional) views and experiences of the prototype I&S resource regarding format, content and delivery of information and support. To achieve this, a user group will be formed (6-10 health professionals) who will provide constant and rapid feedback to the research team and endoscope-i as developments and changes are made.

In addition, the I&S resource will be presented at co-design patient workshop 2, and then revised and re-presented at workshop 3. Workshops 2 & 3 will include approximately 15-20 patients from workshop 1 and approximately 15-20 new patients respectively, who will be recruited using the same methods as the first two workshops. Participants in Workshops 2 & 3 will be asked to use the prototype I&S resource for a week before attending so they have concrete experience of the prototype resource before the workshops. At the workshops, the participants will be asked to complete set tasks to test usability and ensure accessibility and ease of use(59). Participants will also be asked their views on the intervention as a whole, and its acceptability to patients. The prototype of the I&S resource following workshop 3 will be sent to health professionals (n=15-20) from the focus group with HNCs in WS3a to evaluate it in terms of acceptability and feasibility in clinical practice.

Please note that due to the ongoing COVID 19 crisis each workshop will be divided into 3 smaller virtual workshops (n=5-7).

The information and support resource will be available in electronic (web-based and mobile app) and paper based booklet formats to cater for patient preference. Endoscope-i will produce the digital solutions and support resources based on the content supplied. Throughout the focus groups, workshops and other sessions concepts and mockups will be produced for group participation and evaluation which will inform the final design of the content and functions of both the app and website. The information and support resource will include information on: red flag symptoms of recurrence that should trigger the patient to initiate follow-up; self-examination techniques and reminders to conduct self-examination, how to initiate follow-up; how to overcome both perceptual and practical barriers to initiating follow-up; links to HNC peer support groups (e.g. The Swallows, Heads Up, The Throat Cancer Foundation), and cancer charities (e.g. Head and Neck Cancer Foundation, Macmillan, Maggies Cancer Centres, Cancer Research UK); links to existing information and resources about living well after a head and neck cancer diagnosis and managing side effects; contact details of the HNC clinical team, and a symptom diary for the patient to record their symptoms.

### 1.5.4. Population and sampling

*Patients:*

Head and neck cancer patients up to five years post treatment will be recruited via participating HNC clinics, and publicizing through HNC support groups (e.g. The Swallows, Heads2gether) and charities (e.g. Throat Cancer Foundation, Mouth Cancer Foundation, Macmillan, Maggies Cancer Centres, Cancer Research UK). Patients will be recruited by members of their clinical team (e.g. surgeons, oncologists, clinical nurse specialists and AHPs). Patients will be given an invite, PIS and consent form. Patients will be given at least 24 hours to consider participating, and may consent to take part immediately before the workshop commences. If a patient becomes tired during the workshop they will be offered a break and can rejoin the workshop when they feel able.

We will seek to attain a maximum variation sample of patients according to tumour groups, treatment received (surgery versus non-surgical) and educational level. To ensure we have a maximum variation sample and include a diversity of opinions regarding acceptability of the intervention and the information and support resource, we will try to recruit non-English speaking participants in work streams 3a and 3b, and data collect through face to face interviews with a translator present. Translators will be accessed via a range of existing mechanisms e.g. through the Patient Advice and Liaison Services (PALS) in the NHS; translation resources within the participating universities; translation resources offered by relevant charities and support groups; and through participants' family and friends where necessary. If patient recruitment to workshops is poor, alternative approaches will include telephone, videoconference, face-to-face, and for those who have speech problems following treatment for H&N cancer, email interviews.

The questionnaire survey will be distributed via supporting charities and support groups and HNC clinics if needed. No personal identifiable data will be collected; however, descriptive information and limited demographics will be.

*Health professionals:*

HNC health professionals, and other relevant stakeholders who participated in the HNC focus groups in 3a will be contacted again and asked to evaluate the I&S resource and training resource. Consent to contact them for this evaluation will be gained prior to the focus groups in 3a (as part of same consent procedure as 3a).

*Diversity:*

When enrolling non-English speaking participants, the consent form and participant information sheet document will be translated into the participant's native language. We will approach existing black and ethnic minority (BAME) professional, voluntary and PPI groups in participating organisations to provide advice to the study team on addressing issues of equality, diversity and inclusion of non-English speaking participants throughout the study. We will also be guided by the NIHR CLARHC toolkit on 'Increasing participation of Black, Asian and minority ethnic (BAME) groups in health and social care research' (2018).

### 1.5.5. Analysis

Workshops will be video/audio-recorded and transcribed. To ensure that we remain open and grounded in the user's perspective, we will conduct inductive thematic analysis of all textual data(50), and triangulate where appropriate with data from the narrative review. Intervention Development Mapping (Bartholomew 2011) will be used to inform the development of the I&S package.

### 1.5.6. Approval of I&S resource

We will convene another meeting of the Programme Management Group, the Patient Advisory Group and the Clinical Advisory Group to finalise the intervention package and I&S – based on the data obtained from workshops 2 and 3. This will then constitute the intervention and I&S package to be used in the feasibility study. A separate protocol and ethics application will be created for the feasibility trial and RCT.

At this point, the WS3 research team will develop the intervention manual and training package(s) for intervention delivery personnel (HNC clinical nurse specialist or speech and language specialist or dietician). We envisage training will be supported by online resources. This will be co-designed and tested in a further workshop with health professionals that participated in the HNC focus groups in WS3a.

## 1.6. Research Ethics Committee Review and Reports

Before the start of the study, a favourable opinion will be sought from the UK Health Departments Research Ethics Service NHS REC for the study protocol, informed consent forms and other relevant documents. A site-specific form will also be completed via NRES to allow for local R&D approval. Substantial amendments that require review by NHS REC will not be implemented until that review is in place and other mechanisms are in place to implement at site. All correspondence with the REC will be retained and the Chief Investigators will produce the annual reports as required. The Chief Investigators will notify the REC of the end of this component of the programme (i.e. WS3a and 3b). A separate ethics application will be submitted for the ensuing feasibility and randomized trial component of the programme. Annual progress reports (APR) will be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given, and annually until WS3a and 3b have concluded. Within one year after the end of the study, the Chief Investigators will submit a final report with the results, including any publications/abstracts, to the REC.

## 1.7. Regulatory Review and Compliance

Before any site can enrol patients into the study, the PETNECK 2 Programme Manager will ensure that appropriate approvals from each NHS organisation are in place. For any amendment to the study, the Chief Investigators, in agreement with the sponsor, will submit information to each NHS site in order for them to issue approval for the amendment. The PETNECK 2 Programme Manager will work with sites (R&D departments at NHS sites as well as the study delivery team) so they can put the necessary arrangements in place to implement the amendment to confirm their support for the study as amended.

## 1.8. Informed consent and registration

It is the responsibility of the local Site Investigator to obtain informed consent (written or verbal) for each patient prior to participation. The Investigator may delegate the task of obtaining informed consent to an

appropriately qualified research nurse, clinical research practitioner or research fellow trained in obtaining informed consent and in Good Clinical Practice (GCP). However, assessing patient suitability and the final confirmation of patient eligibility is the responsibility of the local Site Investigator. This delegation of responsibilities must be clearly documented on the Site Signature and Delegation Log. To facilitate the informed consent process, there are separate Briefing Summary, Participant Information Sheets (PISs) and Informed Consent Forms (ICFs). Patients will be given at least 24 hours to read the Briefing Summary and PIS and to discuss their participation with others outside of the site research team if they wish to. The patient must be given an opportunity to ask questions which should be answered to their satisfaction. The investigator should also stress that the patient is completely free to refuse to take part or withdraw at any time. The right of the patient to refuse to participate without giving a reason must be respected.

### 1.9. Patient and Public Involvement

We consider constant and consistent PPI involvement throughout this programme to be of paramount importance. Therefore, in addition to the PPI input received to date when developing the programme, a Patient Advisory Group (PAG) has been set up. The Group consists of up to 10 members. Two members will also sit on the Programme Management Group to ensure direct input into decision making and direction of the programme. In addition, members of the PAG will work with the leads of work streams 3a and 3b to directly input into the following activities:

- Advise on the questions and interview guides of WS3a and WS3b
- Review the materials developed for the patient I&S resource and give final approval
- Provide feedback and input on the initial intervention and its iterations, and approve the final intervention to be used in the RCT

In addition to their continuous input into the research activities above, the Patient Advisory Group will formally meet on a regular basis. Members of the PAG will be offered financial compensation in line with NIHR INVOLVE guidelines.

### 1.10. Data protection and confidentiality

All participant confidential information will be handled according to the University of Birmingham's data protection policy (https://www.birmingham.ac.uk/Documents/university/legal/data-prot-policy.pdf). All contact details will be kept in a password protected spreadsheet, which will only be accessible to the researchers conducting the interviews/workshops. This will be stored on a secure computer at the Universities of Birmingham, Bristol and Oxford Brookes, and to a password protected University of Birmingham network space. These details will only be used by the qualitative researchers to recruit participants and arrange interviews. There will be no participant identifiers in files, databases and transcripts. These will only be labelled with study assigned participant numbers. Patient identifiers will not be used when publishing quotations from interviews or audio recordings. Interviews/workshops will be recorded on an encrypted digital recorder which will be locked in a secured cabinet or using secure videoconferencing facilities. All recordings will be coded before transcription and the transcriber will sign a confidentiality agreement. All transcripts and audio recordings will be pseudo-anonymised. Coding keys matching the name of the participants with the ID code will be kept and stored in a password protected spreadsheet. These will be maintained and only be accessed by the immediate research team.

## REFERENCES


1. Ferlay J, Shin H-R, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. Int J Cancer. 2010 Dec 15;127(12):2893–917.
2. CRUK. Head and Neck cancer statistics [Internet]. www.cancerresearchuk.org. [cited 2019 Mar 21]. Available from: https://www.cancerresearchuk.org/health-professional/cancer- statistics/statistics-by-cancer-type/head-and-neck-cancers
3. Semple CJ, Dunwoody L, George Kernohan W, McCaughan E, Sullivan K. Changes and challenges to patients' lifestyle patterns following treatment for head and neck cancer. J Adv Nurs. 2nd ed. 2008 Jul;63(1):85–93.
4. Ang KK, Harris J, Wheeler R, Weber R, Rosenthal DI, Nguyen-Tân PF, et al. Human papillomavirus and survival of patients with oropharyngeal cancer. N Engl J Med. 2010 Jul 1;363(1):24–35.
5. Forastiere AA, Goepfert H, Maor M, Pajak TF, Weber R, Morrison W, et al. Concurrent chemotherapy and radiotherapy for organ preservation in advanced laryngeal cancer. N Engl J Med. 2003 Nov 27;349(22):2091–8.
6. Wensing BM, Merkx MAW, Krabbe PFM, Marres HAM, van den Hoogen FJA. Oral squamous cell carcinoma and a clinically negative neck: The value of follow-up. Head Neck. 2010 Nov 29;33(10):1400–5.
7. Pagh A, Vedtofte T, Lynggaard CD, Rubek N, Lonka M, Johansen J, et al. The value of routine follow-up after treatment for head and neck cancer. A National Survey from DAHANCA. Acta Oncologica. 2013 Jan 16;52(2):277–84.
8. Schwartz LH, Ozsahin M, Zhang GN, Touboul E, De Vataire F, Andolenko P, et al. Synchronous and metachronous head and neck carcinomas. Cancer. 1994 Oct 1;74(7):1933–8.
9. Sturgis EM, Miller RH. Second primary malignancies in the head and neck cancer patient. Ann Otol Rhinol Laryngol. 1995 Dec;104(12):946–54.
10. Zafereo ME, Hanasono MM, Rosenthal DI, Sturgis EM, Lewin JS, Roberts DB, et al. The role of salvage surgery in patients with recurrent squamous cell carcinoma of the oropharynx. Cancer. 2009 Dec 15;115(24):5723–33.
11. Tan HK, Giger R, Auperin A, Bourhis J, Janot F, Temam S. Salvage surgery after concomitant chemoradiation in head and neck squamous cell carcinomas - stratification for postsalvage survival. Head Neck. 2010 Feb;32(2):139–47.
12. Simo R, Homer J, Clarke P, MacKenzie K, Paleri V, Pracy P, et al. Follow-up after treatment for head and neck cancer: United Kingdom National Multidisciplinary Guidelines. Vol. 130, The Journal of laryngology and otology. 2016. pp. S208–11.
13. Joshi A, Calman F, O'Connell M, Jeannon J-P, Pracy P, Simo R. Current trends in the follow-up of head and neck cancer patients in the UK. Clin Oncol (R Coll Radiol). 2010 Mar;22(2):114–8.
14. Kothari P, Trinidade A, Hewitt RJD, Singh A, O'Flynn P. The follow-up of patients with head and neck cancer: an analysis of 1,039 patients. Eur Arch Otorhinolaryngol. 2011 Aug;268(8):1191– 200.
15. Pagh A, Grau C, Overgaard J. Failure pattern and salvage treatment after radical treatment of head and neck cancer. Acta Oncologica. 2016 May;55(5):625–32.
16. Chang J-H, Wu C-C, Yuan KS-P, Wu ATH, Wu S-Y. Locoregionally recurrent head and neck squamous cell carcinoma: incidence, survival, prognostic factors, and treatment outcomes. Oncotarget. 2017 Aug 15;8(33):55600–12.
17. Mabanta SR, Mendenhall WM, Stringer SP, Cassisi NJ. Salvage treatment for neck recurrence after irradiation alone for head and neck squamous cell carcinoma with clinically positive neck nodes. Head Neck. 1999 Oct;21(7):591–4.
18. Richards T. Bring outpatients into the 21st century. BMJ. 2018 Jun 6;361:k2472.
19. Trinidade A, Kothari P, Andreou Z, Hewitt RJD, O'Flynn P. Follow-up in head and neck cancer: patients' perspective. Int J Health Care Qual Assur. 2012;25(2):145–9.
20. https://www.ncri.org.uk/lwbc/all-questions/.
21. Whear R, Abdul-Rahman A-K, Boddy K, Thompson-Coon J, Perry M, Stein K. The clinical effectiveness of patient initiated clinics for patients with chronic or recurrent conditions managed in secondary care: a systematic review. PLoS ONE. 2013;8(10):e74774.

22. Whear R, Abdul-Rahman A-K, Thompson-Coon J, Boddy K, Perry MG, Stein K. Patient initiated clinics for patients with chronic or recurrent conditions managed in secondary care: a systematic review of patient reported outcomes and patient and clinician satisfaction. BMC Health Serv Res. 2013 Dec 1;13:501.
23. Boysen M, Lövdal O, Tausjö J, Winther F. The value of follow-up in patients treated for squamous cell carcinoma of the head and neck. Eur J Cancer. 1992;28(2-3):426–30.
24. Schwartz DL, Barker J, Chansky K, Yueh B, Raminfar L, Drago P, et al. Postradiotherapy surveillance practice for head and neck squamous cell carcinoma--too much for too little? Head Neck. 2003 Dec;25(12):990–9.
25. Kissun D, Magennis P, Lowe D, Brown JS, Vaughan ED, Rogers SN. Timing and presentation of recurrent oral and oropharyngeal squamous cell carcinoma and awareness in the outpatient clinic. Br J Oral Maxillofac Surg. 2006 Oct;44(5):371–6.
26. Flynn CJ, Khaouam N, Gardner S, Higgins K, Enepekides D, Balogh J, et al. Clinical Oncology. Clin Oncol (R Coll Radiol). Elsevier Ltd; 2010 Dec 1;22(10):868–73.
27. Ilmarinen T, Keski-Säntti H, Markkanen-Leppänen M, Haapaniemi A, Tapiovaara L, Atula T, et al. De-escalation of post-treatment surveillance in oropharyngeal cancer. Head Neck. 2018 Dec 23.
28. de Visscher AV, Manni JJ. Routine long-term follow-up in patients treated with curative intent for squamous cell carcinoma of the larynx, pharynx, and oral cavity. Does it make sense? Arch Otolaryngol Head Neck Surg. 1994 Sep;120(9):934–9.
29. PhDa EK, PhDb JD, PhDc RB, MScd PM, Goodwin VA. Bridging the second gap in translation: a case study of barriers and facilitators to implementing Patient-initiated Clinics into secondary care. European Journal for Person Centered Healthcare. 2017 May 19;5(1):129–37.
30. Simard S, Thewes B, Humphris G, Dixon M, Hayden C, Mireskandari S, et al. Fear of cancer recurrence in adult cancer survivors: a systematic review of quantitative studies. J Cancer Surviv. 2013;7(3):300–22.
31. Ghazali N, Cadwallader E, Lowe D, Humphris G, Ozakinci G, Rogers SN. Fear of recurrence among head and neck cancer survivors: longitudinal trends. Psychooncology. 2013 Apr;22(4):807–13.
32. Lebel S, Ozakinci G, Humphris G, Mutsaers B, Thewes B, Prins J, et al. From normal response to clinical problem: definition and clinical features of fear of cancer recurrence. Support Care Cancer. 2016;24(8):3265–8.
33. Campbell BH, Marbella A, Layde PM. Quality of life and recurrence concern in survivors of head and neck cancer. The Laryngoscope. 2000 Jun;110(6):895–906.
34. Koch L, Jansen L, Brenner H, Arndt V. Fear of recurrence and disease progression in long-term (≥ 5 years) cancer survivors--a systematic review of quantitative studies. Psychooncology. 2013 Jan;22(1):1–11.
35. Butow P, Sharpe L, Thewes B, Turner J, Gilchrist J, Beith J. Fear of Cancer Recurrence: A Practical Guide for Clinicians. Oncology (Williston Park, NY). 2018 Jan 15;32(1):32–8.
36. Rogers SN, Cross B, Talwar C, Lowe D, Humphris G. A single-item screening question for fear of recurrence in head and neck cancer. Eur Arch Otorhinolaryngol. 2016 May;273(5):1235–42.
37. Handschel J, Naujoks C, Kübler NR, Krüskemper G. Fear of recurrence significantly influences quality of life in oral cancer patients. Oral Oncol. 2012 Dec;48(12):1276–80.
38. Mutsaers B, Jones G, Rutkowski N, Tomei C, Séguin Leclair C, Petricone-Westwood D, et al. When fear of cancer recurrence becomes a clinical issue: a qualitative analysis of features associated with clinical fear of cancer recurrence. Support Care Cancer. 2016;24(10):4207–18.
39. McGinty HL, Small BJ, Laronga C, Jacobsen PB. Predictors and patterns of fear of cancer recurrence in breast cancer survivors. Health Psychol. 2016 Jan;35(1):1–9.
40. Ozakinci G, Swash B, Humphris G, Rogers SN, Hulbert-Williams NJ. Fear of cancer recurrence in oral and oropharyngeal cancer patients: An investigation of the clinical encounter. Eur JCancer Care (Engl). 2018 Jan;27(1).
41. Jeppesen MM, Jensen PT, Hansen DG, Christensen RD, Mogensen O. Patient-initiated follow up affects fear of recurrence and healthcare use: a randomised trial in early-stage endometrial cancer. BJOG. 2018 Dec;125(13):1705–14.

42. Näsman A, Attner P, Hammarstedt L, Du J, Eriksson M, Giraud G, et al. Incidence of human papillomavirus (HPV) positive tonsillar carcinoma in Stockholm, Sweden: an epidemic of viral- induced carcinoma? Int J Cancer. 2009 Jul 15;125(2):362–6.
43. Mehanna H, Jones TM, Gregoire V, Ang KK. Oropharyngeal carcinoma related to human papillomavirus. BMJ. 2010 ed. 2010;340:c1439.
44. Louie KS, Mehanna H, Sasieni P. Trends in head and neck cancers in England from 1995 to 2011 and projections up to 2025. Oral Oncol. 2015 Apr;51(4):341–8.
45. Van Dyne EA, Henley SJ, Saraiya M, Thomas CC, Markowitz LE, Benard VB. Trends in Human Papillomavirus-Associated Cancers - United States, 1999-2015. MMWR Morb Mortal Wkly Rep. 2018 Aug 24;67(33):918–24.
46. Keeping ST, Tempest MJ, Stephens SJ, Carroll SM, Simcock R, Jones TM, et al. The cost of oropharyngeal cancer in England: A retrospective hospital data analysis. Clin Otolaryngol. 2018 Feb;43(1):223–9.
47. Mehanna H, Wong W-L, McConkey CC, Rahman JK, Robinson M, Hartley AGJ, et al. PET-CT Surveillance versus Neck Dissection in Advanced Head and Neck Cancer. N Engl J Med. 2016 Apr 14;374(15):1444–54.
48. Donovan JL, Rooshenas L, Jepson M, Elliott D, Wade J, Avery K, et al. Optimising recruitment and informed consent in randomised controlled trials: the development and implementation of the Quintet Recruitment Intervention (QRI). Trials. 2016 Jun 8;17(1):283.
49. Rooshenas L, Scott LJ, Blazeby JM, Rogers CA, Tilling KM, Husbands S, et al. The QuinteT Recruitment Intervention supported five randomized trials to recruit to target: a mixed-methods evaluation. J Clin Epidemiol. 2019 Feb;106:108–20.
50. Braun V, Clarke V. Using thematic analysis in psychology. Qualitative Research in Psychology. 2006 Jan;3(2):77–101.
51. Craig P, Dieppe P, Macintyre S, Michie S, Nazareth I, Petticrew M. Developing and evaluating complex interventions: the new Medical Research Council guidance. Int J Nurs Stud. 2013 May;50(5):587–92.
52. Greaves CJ, Wingham J, Deighan C, et al. Optimising self-care support for people with heart failure and their caregivers: development of the Rehabilitation Enablement in Chronic Heart Failure (REACH-HF) intervention using intervention mapping. Pilot and Feasibility Studies 2016;2(37):1-17
53. Michie S, Atkins L, West R. The Behaviour Change Wheel: A Guide To Designing Interventions. London: Silverback Publishing 2014. pp66-69.
54. Yamato T, Maher C, Saragiotto B, Moseley A, Hoffmann T, Elkins M, et al. The TIDieR Checklist Will Benefit the Physical Therapy Profession. Physical Therapy. 2016 Jul;96(7):930–1.
55. FLESCH R. A new readability yardstick. J Appl Psychol. 1948 Jun;32(3):221–33.
56. Kincaid JP, Fishburne RP Jr, Service USNTI, Rogers RL, Chissom BS, BRANCH NTTCMTR. Derivation of New Readability Formulas (Automated Readability Index, Fog Count and Flesch Reading Ease Formula) for Navy Enlisted Personnel. 1975. 1 p.
57. McLaughlin GH. SMOG Grading —– a New Readability Formula. 2006 May 11;:1–8.
58. Bradbury K, Watts S, Arden-Close E, Yardley L, Lewith G. Developing digital interventions: a methodological guide. Evid Based Complement Alternat Med. 2014;2014:561320.
59. Hinchliffe A, Mummery WK. Applying usability testing techniques to improve a health promotion website. Health Promot J Austr. 2008 Apr;19(1):29–35.
60. Bartholomew LK, Parcel GS, Kok G, et al. Planning health promotion programs. An intervention mapping approach. 3rd ed. San Francisco: John Wiley & Sons; 2011.