Study Protocol

Study title: Changes to function and quality of life and patient experience for patients undergoing treatments for recurrent oropharyngeal cancer CCR5242.

Short Title: **FUNQOLR** (**FUN**ctiional and **QOL** changes with **R**ecurrent oropharyngeal cancer)

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1. Background

Approximately 9000 patients are treated for head and neck cancer (HNC) by the NHS every year (Paleri et al 2018). There has been a dramatic increase in oropharyngeal cancer (OPC) over the past 15 years and this in part is due to the rise in Human Papilloma Virus (HPV) related disease (Schache et al 2016). Non-HPV related OPC, which is traditionally associated with a history of smoking and alcohol, is also increasing in the UK (Schache et al 2016). This trend is predicted to continue with an expected 50% rise in HNC cases over the next 20 years (Louie et al 2015).

Primary OPC is treated with curative intent using (chemo) radiation, surgery or a combination of these treatment modalities (NICE, 2016). Dysphagia is one of the most profound side-effects of HNC and/or its treatment, with swallowing ability being a priority concern for patients up to one year following treatment (Roe et al 2014). Dysphagia is an independent predictor of survival and is associated with higher risk of pneumonia, poorer oral intake, prolonged gastrostomy use, poor nutritional status and weight loss as well as fundamental changes to eating patterns, social life, and subsequent quality of life (QoL) (Patterson et al 2016). Speech can also be affected by the presence of a tumour or the treatments received in particular surgical management and this can have a devastating impact on a person's psychosocial well-being, participation in social and occupational roles and overall QoL (Clarke et al 2016).

Despite advances in various treatment modalities, the overall prognosis of HNC patients has not improved significantly within the last several decades and advanced tumours have a recurrence rate of 20–30% at the primary tumour site (Mandapathil et al 2014). Patients may present with residual disease (diagnosed within 12 months of initial treatment) or recurrent disease (diagnosed within 5 years of initial treatment) (Hardman et al, 2020). In addition to residual/ recurrent disease, patients with HNC are also over 11 times more likely than the general population to develop a second primary head and neck cancer (Chuang et al 2008). For patients with second primary HNC disease, this typically occurs in a previously irradiated field including the primary disease site and/or neck and in the radical or adjunctive setting (Hardman et al 2020). Due to the complexity of further treatment in any form, patients with residual, recurrent and new primary disease in a previously irradiated field, are considered a homogenous cohort (Paleri et al 2020) and for the purposes of this document will be referred to as patients with recurrent OPC.

Recurrent OPCs present some of the most challenging management issues in head and neck surgical and oncological practice. Surgery or re-irradiation may be the only hope for locoregional disease control however these treatments may have substantial implications for communication and swallowing function and overall QoL (Mehanna et al, 2016). As a result, the majority of these patients are either treated with palliative intent including chemotherapy, immunotherapy, clinical trial entry or receive best supportive care (Mehanna et al, 2016). However, recent literature has suggested that survival outcomes are improving for patients with recurrent OPC. A recent meta-analysis shows that the outcomes in cases of OPC recurrence appear to have improved significantly over the last two decades, reaching five-year survival of 50 per cent in patients treated surgically

(Jayaram et al, 2016). Improved survival may be the result of a combination of factors including patient selection, advances in surgical care and the role of HPV as a distinct aetiological factor (Mehanna et al, 2016).

The aim of surgical resection in the recurrent setting, also referred to as salvage surgery, is complete macroscopic clearance of the recurrent tumour with wide clear margins which can result in large defects which require reconstruction (Mehanna et al 2016). This can have a significant functional impact on communication and swallowing and overall QoL (White et al, 2013). The consequential large functional deficits must be balanced against the benefit of longer survival (Mehanna et al, 2016). Open salvage surgery for recurrent OPC has been associated with a high complication rate with 48% patients experiencing poor healing and prolonged hospital stays (Zafereo et al 2009). Successful resection of OPC recurrence can be difficult due to the complex three-dimensional anatomy and proximity and adherence to the internal carotid artery (Mehanna et al 2016). Access procedures through mandibulotomy (jaw split) or lingual release (lip split) are usually required and in the setting of previous radiotherapy this can increase the risk of osteoradionecrosis, in addition to extensive disruption to the oral cavity and floor of mouth musculature (Hamilton & Paleri, 2017). Recent advances in transoral robotic surgery (TORS) have facilitated transoral access to the oropharynx avoiding the need for mandibulotomy or lingual release (Hamilton & Paleri, 2017). The use of this minimally invasive surgical approach is now being extended to the treatment of recurrent OPC (Paleri et al 2020). A recent multicentre case control study showed that salvage patients treated with transoral robotic surgery had a significantly lower incidence of tracheostomy, feeding tube use, and shorter hospital stay, with significantly decreased incidence of positive margins and significantly higher survival than matched patients treated with open surgery (White et al 2013). Favourable outcomes in terms of swallowing recovery have also been reported (Paleri et al 2020).

In the era of highly conformal radiotherapy techniques such as intensity-modulated radiotherapy (IMRT), there may be opportunities for re-irradiation, however this is associated with toxicity and has the potential to further compound pre-existing treatment related effects including swallowing function (Brady et al, 2020).

Patients receiving best supportive care have an average overall survival of four months after diagnosis (Mehanna et al 2016). As per national guidelines, patients with non-resectable recurrent OPC being considered for palliative systemic treatments should be offered the opportunity to participate in clinical trials of new therapeutic agents (Mehanna et al 2016). Triple therapy with platinum, cetuximab and 5-fluorouracil (5-FU) (EXTREME regimen) appears to provide the best outcomes for the management of patients with recurrence who have a good performance status and are fit to receive chemotherapy (Mehanna et al 2016). In a large multisite retrospective review including 733 patients across 71 sites, for patients treated with platinum-based combinations, overall survival was 8 months (95% CI: 7.0 – 8.0), with 1-year survival reaching only 30.9% (95% CI 27.5 – 34.3) (Grünwald et al 2020). More recently, however, the results of the KEYNOTE-048 study have shown that selected patients experience better survival outcomes and less toxicity with single-agent pembrolizumab or combined pembrolizumab-chemotherapy when compared with the EXTREME regimen (Burtness et al 2019).

National guidance recommends that patients with recurrent HNC should undergo appropriate and extensive counselling regarding expected survival and functional outcomes for treatments for recurrent disease (Mehanna et al, 2016). However, empirical multidimensional functional outcome data is not available for these patients and such data may aid treatment decision making if there are particular concerns regarding function. Given ongoing advancements in the treatment options for recurrent OPC with evidence of improved survival outcomes, these patients are now living longer. However, not only are they living with the well documented treatment effects of their primary treatment (Roe et al 2014), these difficulties are now potentially compounded and exacerbated by further radical surgery, re-irradiation or systemic and targeted therapies.

2. Rationale

To enable people to make informed choices about the range of treatments available for recurrent OPC, detailed information is required on the likely trajectory of functional and QoL change during or following treatment. Patient experience data is essential for any research so that relevant QoL endpoints can be identified, appropriate outcome data can then be collected and thus meaningful data can be presented to patients during the decision-making process (Blanchard et al 2016). This project will aim to address the gaps in the literature with regards to both functional and QoL outcome data and patient/ carer experience of the functional changes in communication and swallowing and overall QoL during and following treatments for recurrent OPC.

The purpose of this study is to understand the lived experience of being diagnosed and living with recurrent head and neck cancer and how functional and QoL changes are prioritised by patients. This study will also measure the trajectory of swallowing, communication and QoL change for people undergoing treatments for recurrent OPC.

3. Aims

1. To report on functional and QoL outcomes for patients who undergo treatments for recurrent OPC including surgery (open or TORS), re-irradiation, palliative systemic or targeted therapies.
2. To describe patient and carer experience of recurrent OPC and priority concerns with regards to function and QoL.

4. Study Design

This study is an exploratory observational design.

This study will comprise of two work streams including:

1. Part A: prospective non-randomised, non-interventional descriptive observational cohort study
2. Part B: a non-interventional, non-randomised longitudinal qualitative descriptive interview study using thematic analysis

Please see figure 1 for study schema.

Population

Part A: patients with biopsy proven residual, recurrent or new primary OPC in a previously irradiated field.

Part B: patients with biopsy proven residual, recurrent or new primary OPC in a previously irradiated field, and their carers.

5. Study objectives

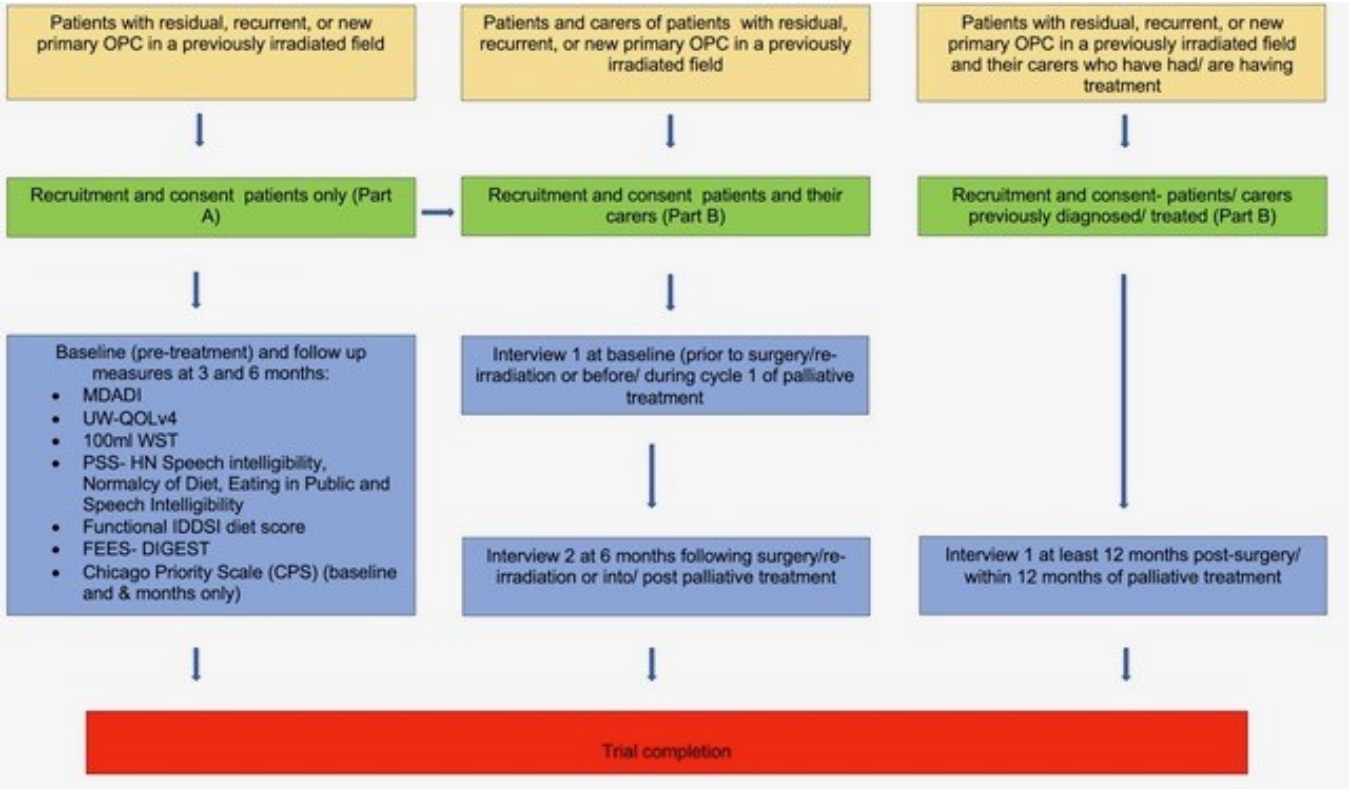
The primary objective of the study is to measure change in swallowing function over time for patients receiving treatment for recurrent OPC which will be evaluated by a patient-reported outcome (PRO) using the MD Anderson Dysphagia Inventory (MDADI) (Chen et al 2001) comparing change from baseline to 6 months.

Secondary objectives for the study are to:

1. Investigate potential changes in function for up to 6 months using
    (i) The Performance Status Scale for Head and Neck Cancer (PSS- HN) scale (normalcy of diet, eating in public and understandability of speech scales) (List et al 1990)
    (ii) the 100 mL Water Swallow Test (100ml WST) (Patterson et al 2011)
    (iii) the International Dysphagia Diet Standardisation Initiative (IDDSI) functional diet score (Steele et al 2018)
    (iv) Fibreoptic Endoscopic Evaluation of Swallowing Dynamic Imaging Grade of Swallowing Toxicity (FEES DIGEST) grade (Starmer et al, *in press*)
2. Assess patient-reported QoL and priority concerns using the University of Washington Quality of Life (UW-QoL) questionnaire (v.04) (Rogers et al 1999)

3. Assess patient-reported priorty concerns at baseline and 6 months using the Chicago Priority Scale (CPS) (Sharp et al 1999)
4. Report on gastrostomy tube usage up to 6 months
5. Report on survival status up to 6 months
6. To explore patient and carer priority concerns with regards to function and QoL and how these concerns may influence decision making regarding treatment options using semi structured interviews

Figure 1: Study schema



6. Study end points

Primary and secondary endpoints for Part A non-interventional descriptive observational cohort study are as follows:

Primary endpoint

Difference in the mean MDADI composite score at baseline compared to 6 months after surgical treatment or re-irradiation or 6 months into non-surgical treatment

Secondary endpoints

1. MDADI composite score at baseline and 3 and6, months following surgical or re-irradition treatment or 3 and 6, months into non-surgical treatment.
2. Mean PSS-HN Normalcy of diet, public eating and speech intelligibility using the PSS-HN scale scores at 3 and 6 months .
3. Median (IQR) IDDSI functional diet score International dysphagia diet standardisation initiative functional diet scale (IDDSI-FDS) at baseline and 3 and 6 months following surgical or re-irradition treatment or 3 ad 6,months into non-surgical treatment.
4. Mean 100ml WST capacity score score at baseline and 3 and 6, months following surgical or re-irradition treatment or 3 and 6 months into non-surgical treatment.
5. FEES DIGEST summary score at baseline and 3 and 6 months following surgical or re-irradition treatment or 3 and 6months into non-surgical treatment.
6. Mean UW-QoL4 composite physical, social and functional scores at baseline and 3 and6 months following surgical or re-irradition treatment or 3 and6 months into non-surgical treatment.
7. Number and percentage of patients ranking of CPS categories (1-12) in order of importance, at baseline and 6 months following surgical or re-irradition treatment or 6 months into non-surgical treatment
8. Number and percentage of patients still alive at the end of the study
9. Number and percentage of patients using a gastrostomy at each time point at baseline and 3 and6 months following surgical or re-irradiation treatment or 3 and6 months into non-surgical treatment.

7. Inclusion/ exclusion criteria

Please see table 1 for inclusion/ exclusion criteria for patient participants in Part A and Part B:

Table 1: Inclusion/ exclusion criteria Part A and B (patient participants)

Inclusion criteria	Exclusion criteria
• Adult (aged 18 years or over) and competent to provide consent	• Any previous medical condition, other than HNC, which has a known impact

• Have a diagnosis of recurrent OPC • Have adequate linguistic and cognitive function to participate in interview • English speaking	on communication/ swallowing (Parkinson's Disease, Multiple Sclerosis, cerebral vascular accident (CVA)

Please see table 2 for inclusion/ exclusion criteria for carers in Part B:

Table 2: Inclusion/ exclusion criteria carers Part B

Inclusion criteria	Exclusion criteria
• Be carers of patients 18 years or over who have been diagnosed with recurrent OPC • Have adequate linguistic and cognitive function to participate in interview • English speaking	• They do not fulfil all of the inclusion criteria

Number of participants

Part A: 44 retrospective participants will be recruited. Please see section 10 for detailed description of statistical plan including sample size calculation.

Part B**:** Expected recruitment rates include approximately 20-30 patients (10-15 retrospectivepatients and 10-15 prospective patients) and 10-20 carers (5-10 carers of retrospective patients and 5-10 carers of prospective patients) or until data saturation occurs- please see data analysis plan in section 11.

8. Methodology

Identification of patients

Sequential patients who are referred to RM for management of newly diagnosed recurrent OPC will be identified from the weekly head and neck multidisciplinary team meeting. Those patients identifying all of the inclusion criteria and who are invited to an appointment at the Royal Marsden will be sent an initial letter of invitation prior to their appointment. At their appointment they will be approached to take part in the study.

Patients who have undergone surgery at least 12 months ago or who have commenced palliative treatments within the last 12 months will be identified from outpatient clinic lists and will be invited to take part in semi structured interviews investigating their experience of being diagnosed with and

treated for recurrent OPC. Carers/ family members of the person with recurrent OPC will also be invited to take part in an interview. Participant identification centres (PICs) will also be used as part of the recruitment strategy for the study. These centres will identify potential participants through database searches and direct these patients to the recruiting site for participation.

Sampling

Purposive sampling will be used to try and recruit patients who are undergoing/undergone the various treatment options available- open surgery, TORS, re-irradiation, palliative systemic treatments, to ensure that there is a range of patients, both male and female, with representation across a range of ethnic and socioeconomic backgrounds for both Parts A and B of the study.

Informed consent

Potential participants who are receiving care at the Royal Marsden will receive a letter of invitation prior to their next scheduled appointment highlighting that they may be approached about the study in advance of their appointment.

At the patients next scheduled outpatient appointment; which may be virtualor face-to-face, their usual care team will introduce the trial with the patient. PICs will also identify potential participants through database searches and direct these patients to the recruiting site for participation. If the patient expressed an interest in being involved, they will be provided with a Patient Information Sheet (PIS) which will include a telephone number and contact email. Patients identified by PICs will be advised to contact the research team using the contact details included in the PIS. Appropriate time will be given to patients and carers to read and digest the information on the PIS. The potential participant may be asked to provide informed consent following a minimum of 1 hour to read the PIS and consider participation. Potential participants will be offered video call facilities to discuss potential participation with their family friend/ relative if they wish.

During the COVID19 pandemic, national guidelines have advised to minimise face-to-face contact with patients and recommended remote consultations. As such, both during the pandemic and for the remainder of the trial, this consent consultation may either be a face-to-face or telephone / video consultation. For participants identified and recruited via PICs – remote consent only will be obtained.

If a remote consent consultation is held patient identification using date of birth and address will be checked during this process. Where possible, there will be two members of the clinical team present for this consultation; one member taking consent and another member present as a witness; however, this is not mandatory for the consent process.

If the patient is eligible, they will be invited to voluntarily provide informed consent to participate in this study. Consent will be taken by a member of the research team/ speech & language therapy team/ research nurse under the supervision of the PI. If the consultation is being conducted face-to-face then consent will be obtained in-person with wet ink signature on the consent form. For remote

telephone / video consultations, verbal consent will be sought and clearly documented in the patients' medical notes. The patient will also be asked to sign a consent form which can be returned to the study team via:

- Post
- Email (the patient should bring the original wet ink copy to their next hospital appointment)
- In person at the patients next face-to-face hospital appointment

Where a patient has been remotely consented, upon receipt of the original wet-ink consent form it will be signed by the member of staff who had discussed the study with the patient and obtained the verbal consent.

At the next possible in-person visit with the RM patient the study team member who carried out the remote consent should countersign the consent form in the presence of the patient. The patients' medical records should be updated to document the entire consent process.

A copy of the signed ICF along with a copy of the PIS will be given to the study participant. An original signed & dated consent form will be scanned and uploaded to the Electronic Patient Record (EPR) for RM patients and a copy will be placed in the investigator site file (ISF).

Subject withdrawal criteria

A participant can withdraw from the study at any time. No further data will be collected but data previously collected will still be used. Participants will be made aware that their overall medical care will not be affected if they choose not to participate/withdraw from the study at any time.

9. Data Acquisition

Part A

Following informed consent, patients will have all functional and QoL measures collected at their next scheduled outpatient appointment. No additional outpatient appointments or patient contacts will be required for RM patients. All patients are routinely seen by the clinical team at baseline, and for regular follow up including 3 and 6 month clinical reviews, where all measures except the Chicago Priority Scale (CPS) will be repeated. The CPS will be completed at baseline and 6 months only. In the event that social distancing measures remain in place and patients are not attending the hospital for face-to-face review with their clinical team, or if the patient has a preference for remote review, and for participants identified via PICs, a video consultation will be set up so that a minimum set of outcome measures can be collected including the MDADI, and UWQoL4, PSS- HN (all domains), Functional IDDSI Diet Score, CPS and the 100ml WST.

The only measure which cannot be obtained via remote means is the FEES assessment. Please see figure 2 for data acquisition schema.

Figure 2: Data acquisition process Part A (face-to-face)

Patient self-administered/ reported	Clinician- reported	Clinical examination
• MDADI • UW-QOL V4.0 • CPS	• PSS-HN • Functional IDDSI Diet Score	• 100ml WST • FEES-DIGEST

Table 3: Data acquisition process Part A (remote consultation)

Patient self-administered	Clinician- reported	Clinical examination
• MDADI • UW-QOL V4.0 • CPS	• PSS-HN • Functional IDDSI Diet Score	• 100ml WST

Please see below a description of each data collection tool:

1. The MDADI is a validated and reliable self-administered questionnaire for evaluating the impact of oropharyngeal dysphagia on QoL in HNC patients. The questionnaire consists of 20 questions. Patients rate their responses to statements included on the MDADI on a 5-point scale from “strongly agree” to “strongly agree”. There are 5 subscales. The first is a single, global subscale question to understand the impact of swallowing problems on quality of life. The other subscales address emotional, functional, and physical problems. The global question is scored individually and the other subscales are scored and the mean score is calculated. The mean score is then multiplied by 20 to calculate the composite total score which can range from 0, indicating very low functioning, to 100, indicating extremely high functioning.
2. The PSS-HN is a clinician rated instrument where each subscale (Normalcy of Diet, Eating in Public and Speech Intelligibility) is rated from 0 to 100, with higher scores indicating better performance. The PSS-HN has been shown to have good inter-rater reliability and sensitivity to differences in performance and change over time. See appendix 1 for standard operating procedure.
3. The IDDSI functional diet score is a clinician rated measure of dysphagia severity based on the degree of diet texture restriction. See appendix 2 for standard operating procedure.
4. The 100ml WST is a simple, repeatable measure of swallowing efficiency. This measure has been previously validated in the head and neck population, and the quantitative measures derived from this test, can be used as a measure of swallow performance over time. Patients are asked to drink 100ml of water as quickly and as comfortably as possible- swallow volume, capacity and speed are calculated by timing the test and counting the number of swallows completed by the participant. See appendix 3 for standard operating procedure.
5. The DIGEST-FEES is a rating scale used to report on swallowing safety and efficiency as observed during a Fibreoptice Endoscopic Evaluation of Swallowing (FEES). FEES is an SLT led

endoscopy procedure which involves the use of a fibreoptic scope which is passed transnasally into the participant's pharynx by a trained SLT. The patient is given some food and liquids so that swallowing function can be measured in terms of swallowing safety and swallowing efficiency. The summary DIGEST rating aligns with National Cancer Initiative's framework for toxicity reporting in oncology trials and assigns a global rating of pharyngeal swallowing function according to the interaction of the safety and efficiency profile scores. See appendix 4 for standard operating procedure.

6. The UW-QOL v4.0 is a validated QoL tool examining 12 QoL domains including pain, appearance, activity, recreation, swallowing, chewing, speech, shoulder function, taste, saliva, mood and anxiety. In this tool, each question is scaled from 0 (worst) to 100 (best) according to the hierarchy of response. It also has two global questions about their health-related and overall QoL. In addition, it is possible to calculate a composite score of physical and social-emotional functioning (Rogers et al 1999). The UW-QOL questionnaire is a self-administered scale and each of the categories has several options within it that allow the patient to describe their current functional status. Patients also have the opportunity to select up to 3 options from the 12 domains that are most important to them. The questionnaire relates to the previous 7 days.
7. The CPS is a previously validated tool to assess patients' priorities among potential functional outcomes following treatment for head and neck cancer. Participants will be given a list of 12 statements; including 'being cured of my cancer', 'living as long as possible', 'having no pain', 'being able to swallow all foods and drinks', 'having a normal amount of energy for me', 'returning to my activities as soon as possible', 'having my speech understood easily', 'keeping my natural voice', 'having a comfortably moist mouth', 'keeping my appearance unchanged', 'being able to chew normally' and 'keeping my normal sense of taste and smell'. Patients will be asked to rank each priority from 1-12 where the most important priority is ranked number 1 and the least important number 12.

The multi-dimensional outcome measures will include all routine measures of swallowing function used at our centre currently. The UW-QOL V4.0 and CPS assessment will be in addition to standard of care assessment by the SLT team.

Please see table 4 for data acquisition plan:

Table 4: data acquisition time points part A

Timepoint	Measure	Domain	Endpoint
Baseline, 3, and 6 months	MDADI	Swallowing related QoL	Composite score
	UW-QoLv4	Health related QoL	Composite scores of physical and social-emotional functioning are derived from 12 domains. Patients can also highlight up to 3

			priority concerns from the previous 7 days
	PSS-HN	Normalcy of Diet, Eating in public and speech intelligibility	Score for each subset
	100ml WST	Swallowing function	Swallowing capacity score (mls/second)
	Functional IDDSI diet score	Diet modification	Diet score (1-8)
	FEES- DIGEST (only if patient is attending for a face-to-face appointment	Swallowing toxicity rating	Summary score (0-4)
Baseline & 6 months	Chicago priority scale	Patient priority rating of treatment outcomes	Ranked 1-12 priorities

Part B

Following informed consent, a proportion of the sample in Part A (prospective cohort), a number of patients who have undergone surgery at least one year ago/ or commenced palliative treatments within the past 12 months (retrospective cohort) and also carers from both patient cohorts will be invited to take part in interviews via video consultation. The interview with patients/ carers will take place at a time that is convenient to both the patient and carers. Participants to be included in Part B will also be identified via PICs.

For the prospective patient cohort who are also participating in part A of the study the interview will take place after the measures have been collected in Part A on a day which is convenient to the participants. Semi-structured interviews will be completed with a member of the research team and will include a number of questions detailed in the topic guide directed towards the research aim in order to promote discussion and identify key swallowing, communication and QoL priorities and concerns. The topic guide has been developed from previous literature and via consultation with the project's Patient-Public Steering Group (please see section 13 on PPI). For the prospective cohort the interview will be completed at baseline and again at 6 months following or into treatment.

For the retrospective cohort the interview will take place for both patient and carers at a single timepoint at least 12 months post surgery or within 12 months of commencing palliative treatments.

The interviews will take place remotely either via telephone or video consultation. The interviews will be anonymised and transcribed verbatim. Please see section 11 for description on how the data will be analysed.

10. Sample size

Part A

Part A: The sample size calculation is based on the primary endpoint, change in MDADI scores from baseline and 6 months following diagnosis/treatment of recurrent disease. Previous data has shown that a 10-point between-group difference in MDADI score is clinically significant (Hutcheson et al 2016). This end point has not been measured systematically previously in recurrent disease patients.

Pilot data collected at the Royal Marsden Hospital available for a service evaluation was used to look MDADI score in this cohort of patients. Data based on 10 patients shows a mean composite score of 66.50 at baseline and 52.60 at 6 months with a standard deviation of the difference of 23.68.

With a two-sided alpha of 5% and 95% power a total of 40 participants will be required to complete the paired questionnaires at baseline and 6 months post-treatment (power function, STATA). An additional 4 patients will be recruited to cover for 10% drop out for a total sample of 44 patients. Seventy-five patients are referred to the Royal Marsden Hospital per year with recurrent OPC and this number is set to increase with the on-going developments in robotic surgery, experimental trials and the development of the International Centre for Recurrent Head and Neck Cancer (IReC). Data collection will take place over an 18-month period.

Part B

Given that this study is qualitative and exploratory, a sample size calculation is not required. Expected recruitment rates include approximately 20-30 patients and 10-20 carers or until data saturation occurs- please see data analysis plan in section 11.

11. Data analysis

A consort flow diagram will be produced to describe the flow of patients through the study

Part A

Baseline patient characteristics (age, gender, ethnicity and previous HNC treatment history) will be summarized in addition to the diagnostic and treatment details (site of recurrence, type of treatment, use of reconstruction, tracheostomy, feeding tube presence/ type) using descriptive statistics.

The primary endpoint data will be analysed to compare the mean change from baseline MDADI composite score to 6 months into or post treatment using a two-sided paired t-test if data are normally distributed. In the eventually of not normally distributed data non-parametric-methods (Wilcoxon Signed Rank test) will be used.

Secondary endpoints (PSS, 100ml WST, IDDSI functional diet score, FEES-DIGEST and UW-QOL,and CPS scores) will be summarised using summary statistics (mean with standard deviation if data are normally distributed or median with IQR if data have a skewed distribution).
Counts and percentages will be presented with 95% confidence intervals.

Part B

Framwork theamatic analysis (Iliffe et al 2015) will be used to analyse the qualitative data using NVivo software. The 5 key stages of framework analysis will be used as follows:

1. Familiarisation: data will be sensitised into early themes, individual difference within and between transcripts will be identified
2. Identifying a thematic framework: key themes, issues and discussion points will be identified and given a code/ label
3. Indexing: transcripts will be annotated numerically in order to identify a consistent coding framework
4. Charting: the final coding framework wil be synthesised and developed
5. Mapping and interpreting: the main themes identified from the data will be represented pictorially/ graphically to demonstrate how they interact with and relate to each other

12. Patient and public involvement

This research proposal was presented to the Patient and Carers Research Review Panel at the Royal Marsden Hospital on 16.1.2019. This group included two HNC patients, one of whom has recurrent disease, carers and lay volunteers. The NIHR Research Design Service (RDS) Enabling Involvement Fund was also awarded to the research team to further involve patients and carers in the design of this study. Using this initial funding a small group of patients who have undergone treatment for recurrent OPC were invited as a PPI research steering group specific to this project. A meeting with this group was held on 22.2.2019. Two of the patients attended and a further four provided feedback and advice remotely. The research proposal was presented for discussion. This research has also been discussed with Mr Chris Curtis, Chair of the Swallows Head and Neck Cancer Charity. Opinions were sought on the research idea/question and the data collection methods including interviews and proposed functional outcome measures.

The PPI groups explained the following:

- The research question was *'important'* and *'worthwhile'* and commented on the importance of capturing information about functional outcomes *'I would have found information on*

speech and swallowing very helpful in my decision making...I didn't have that information and that was what I was worried about'

- It was crucial to use interviews in addition to functional outcome measures, as 'not all information can be captured by clinical tools'
- Carers should be included as interviewees, as key functional concerns and QoL concerns will impact carers too. They explained that communication and eating and drinking '*is social*' involving '*more than just the patient*' and that *'patients and families "hear" different things'*, *'the diagnosis, treatment and aftermath have such an impact on the family as a whole'.*
- The outcome measures outlined in the research proposal were '*acceptable'*, including objective measures which are sometimes 'reassuring'; *'I seem to be able to tolerate nasendoscopy fairly well and find it helpful and reassuring to know what is going on with my swallow'.*

The research protocol was delayed due to the pandemic however co-investigator kept in touch with the core PPI group of patients with a history of recurrent OPC and they continue to work with GB on an ongoing basis with ongoing research planning. At a recent meeting (17.3.21) the primary and secondary objectives and endpoints were revised and approved by the group. The topic schedule for the qualitative study was also developed. The ethics application was also discussed and advice sought on timing of informed consent and any potential psychological distress which might happen as a result of the data collection. The group once again highlighted that having the measures taken may be 'reassuring' and that the interviews may 'give a chance to have your voice heard'.

Wider PPI was sought in March 2021 to review the informed consent form (ICF) and participant information sheet (PIS) using the RM PPI database.

PPI plans throughout the research and dissemination phases are as follows (to be completed remotely via email and videoconferencing):

- Recurrent OPC PPI group now established (6 members). We have agreed 6 monthly virtual meetings with 6 weekly email updates. PPI involvement will include interpretation of results, planning for and write up of results including co-authorship, co-presenting and liaison with charities (for example The Swallows) and patient groups.
- Wider PPI involvement will also be sought using the RM/BRC digital voices platform- an overview and eventually the findings of the study will be presented here.
- The overall findings of the study will be presented back at the Patients and Carers review committee to seek further ideas/ advice on dissemination to patient/ carer groups.

13. Study organisation/ Trial Monitoring and Management Strategy

Responsibilities

Name	Professor Vinidh Paleri

Role(s)	Principal investigator & Chief investigator
Responsibilities	Oversight of project design, conduct and reporting. Liaison with Research Ethics Committee (REC), and other review bodies, during the application process, and where necessary during, the conduct of the research. Ensure adherence to protocol.

Name	Dr Justin Roe
Role(s)	Co-investigator
Responsibilities	Oversight of the clinical outcome data collection. Quality assurance. Ensure adherence to protocol.

Name	Grainne Brady
Role(s)	Co-investigator Research Fellow
Responsibilities	Screening and recruitment including informed consent Data collection: CRF, functional and quality of life outcomes Data collection: qualitative interviews Statistical analysis of quantitative findings Thematic analysis of qualitative findings Project write up and dissemination

Name	Professor Pernilla Lagergren
Role(s)	Co-investigator
Responsibilities	Ensure adherence to protocol. Support analysis of patient reported outcome

Name	Professor Mary Wells
Role(s)	Co-investigator
Responsibilities	Ensure adherence to protocol. Oversight of qualitative methodology.

Data quality checks

Part A: One of the co-investigators who is not involved in the data collection will check the accuracy of 10% of all of the anonymised data entered into the excel spreadsheet.
Part B: One of the co-investigators will review 10% of the anonymised interview transcripts to verify coding process.

Timeline

The protocol will be submitted for scientific review by the Committee for Clinical Research and for local management R&D approval and REC. The PI/CI will be notified in writing of the CCR/ R&D Approval. The study will then be activated on the Hospital Information System and the PI/CI will be notified that the study is open for recruitment. This date will be classified as start date for the R&D database.

The data collection period will continue for 18 months or until 44 patients have been recruited and longitudinal data obtained and 15-20 patients and 12-15 carers have taken part in 2 interviews at baseline and 6 months.

14. Safety reporting

This is a non-invasive study involving routine clinical assessments of function and validated questionnaires designed to identify the presence and symptoms of dysphagia/ communication difficulties and the impact on QoL. Due to the non-interventional nature of the study, adverse events will not be recorded.

The participant may present with a dysphagia. If dysphagia is identified, referral for SLT assessment will be made and the medical team and G.P. informed. Other issues may also arise such as compromised nutritional status or psychological distress. If such issues arise appropriate referrals will be initiated following liaison with the medical team i.e. Dietitian referral, Psychological Support etc.

Participation in interviews/ questionnaires may cause potential upset or emotional distress. The participant's cancer key worker (Head and Neck CNS) will be aware of the patient's participation and will be available to provide psychological support in the event that the participant becomes upset.

15. Regulatory & Ethics Committee Approval

The study will be reviewed by the Committee for Clinical Research (CCR) and the Health Research Authority (HRA). HRA approval conditions will be followed.

16. Data handling and record keeping

All data will be handled in accordance with the UK General Data Protection Regulation (UK GDPR) and the Data Protection Act 2018. The CRFs will not bear the participant's name or other directly identifiable data. The participant's study Identification Number (PIN) only, will be used for identification. The Subject PIN log will be used to cross reference participant's identifiable information. All data from the paper CRFs and questionnaires will be collected in an excel spreadsheet using PINs only.

The ISF and excel spreadsheet, will be stored at the Royal Marsden NHS Foundation Trust. All data will be coded and no identifiable reference to the participants will be held with the data. Paper CRFs and questionnaires and interview transcripts will be stored in locked, fireproof file cabinets. Coded data held electronically will be stored on password protected NHS computers. In the event of remote working, the secured RM sharedrive can be accessed and used by members of the research team employed by the Royal Marsden. Anonymised audio interview data will be transferred securely to an external transcription service.

The investigator site file will include ICFs, questionnaire response forms, and CRFs. The questionnaire responses and CRFs will not bear identifiable information as the anonymous study identification (PIN) number will be used. The ICFs will be stored securely separate to the anonymised data in a locked fire proof filing cabinet held in the SLT department at the Royal Marsden Hospital.

The Royal Marsden NHS Foundation Trust will permit study-related monitoring, audits, REC review, and regulatory inspection(s), providing direct access to source data/documents. Participants are informed of this during the informed consent discussion. Participants will consent to provide access to their medical notes

17. Financing, Indemnity & Insurance

This study will form part of a PhD training fellowship, being undertaken at Imperial College London by a student who is employed by the Royal Marsden NHS Foundation Trust, as Clinical Lead Speech and Language Therapist. The Clinical Doctoral Research Fellowship has been funded by the National Institute of Health Research. The study is supported by The Royal Marsden NHS Foundation Trust. Where the Royal Marsden NHS Foundation Trust is either sponsoring or collaborating with externally sponsored research the NHS Litigation Authority will cover standard clinical negligence by employees, staff and health professionals employed by the Royal Marsden NHS Foundation Trust. For more information visit the following website:
http://www.nhsla.com/Claims/Pages/Clinical.aspx.
There is unlimited liability and no excess. Insurance is provided under the Clinical Negligence Scheme for Trusts and there is no cover for non-negligence claims.

18. Publication policy

The PI is responsible for approving the content and distribution of all publications, abstracts and presentations arising from the study and for assuring the confidentiality and integrity of the study. The data arising from the project will belong to the RMH and will be retained and stored securely with the Royal Marsden NHS Foundation Trust for a period of 5 years.

Any communication arising from this research that enters the public domain, including publications, press releases, websites, presentations, posters and participant materials **correctly acknowledge the NIHR and use the new NIHR identity and will acknowledge support from the BRC.**

Publication: "Any activity that discloses, outside of the circle of trial investigators, any final or interim data or results of the study or any details of the study methodology that have not been made public by the Sponsor including, for example, presentations at symposia, national or regional professional meetings, publications in journals, theses or dissertations."

All scientific contributors to the study have a responsibility to ensure that results of scientific interest arising from Trial are appropriately published and disseminated. The Sponsor has a firm commitment to publish the results of the Trial in a transparent and unbiased manner without consideration for commercial objectives.

To maximise the impact and scientific validity of the study, data shall be consolidated over the duration of the trial, reviewed internally among all investigators and not be submitted for publication prematurely.

19. Abbreviations

Acronym	Meaning
CCR	Committee for clinical research
CI	Chief investigator
CRF	Case report form
GCP	Good clinical practice
HNC	Head and neck cancer
HPV	Human papilloma virus
IRAS	Integrated research application system
ISF	Investigator site file
MDADI	M. D. Anderson Dysphagia Inventory
MDT	Multidisciplinary team
OPC	Oropharyngeal cancer
PI	Principal investigator
PPI	Patient and public involvement
PIN	Patient identification number
PSS-HN	Performance status scale for head and neck cancer
QoL	Quality of life
R&D	Research and development
REC	Research ethics committee
RM	Royal Marsden
SLT	Speech & Language Therapist/Therapy
SOP	Standard operating procedure
UWQoL4	University of Washington Quality of Life Questionnaire
WST	Water swallow test

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Appendix 1: Performance Status Scale in Head and Neck cancer standard operating procedure (SOP)

Purpose:
To describe the procedures employed when evaluating the Normalcy of Diet, Place of Eating and Understandibility of Speech scores using the Performance Status Scale for Head and Neck Cancer (PSS-HN).

Scope:
This SOP outlines the procedure to be carried out by the co investigator or trained Speech and Language Therapists (SLTs), performing the PSS-HN.

Procedure:
Timing of assessments
The PSS-HN assessment is to be carried out at the time points as specified in the protocol: at baseline, and at 3, 6, and 12 following diagnosis. The PSS-HN assessment is to be carried out after completion of the patient reported outcomes, to avoid bias on self-reporting, but before the instrumental FEES assessment.

Assessor
The PSS-HN assessment should only be performed by appropriately trained staff including a member of the research team or trained SLT.

Assessment
It is anticipated that the PSS-HN assessment will take approx. 5 minutes to complete.
Scores for the PSS-HN assessment are determined following an unstructured interview. The scores range from 0 to 100, with higher scores indicating better performance. There are separate scores for each of the 3 subscales. The subscales with the various food items and options can be found in the associated guidance document.
Interviewer instructions for the three subscales are outlined below.

Normalcy of diet
It is recommended that the assessor begins by asking the patient what kinds of food they have been eating, and what foods have been difficult to eat. Based on the patient's response, an item should be chosen at the low end of the scale.
The assessor should move up the scale giving examples of foods in each category, asking the patient whether they are eating these foods. Even if a patient states they eat everything, enquiries should be made about specific items beginning with score 50 (soft chewable foods) and move upwards.
The assessor should stop at an item at, and above, which the patient cannot eat. The patient receives the score below this item.
If the patient eats a full diet, an enquiry should be made if the patient needs to drink more liquids than usual with meals. Eating a full diet with intake of extra fluids is scored 90.

If the patient can take foods orally, but is also using a feeding tube, the score should be based on solid foods and indicate that a feeding tube is used.

Public eating

The patient should be asked:

- where they eat – in a restaurant, at home, at friends/relatives' homes, etc.
- with whom they eat – always alone, with family/friends, etc.
- if they choose different foods when eating with others – softer, less messy, etc.
- when was the last time they ate in a restaurant, MacDonald's, picnic, family reunion.

The score beside the description that best fits the patient should be chosen. A patient on a restricted diet (e.g. tube feeding, pureed foods) who does not eat in public but will join others in a public eating setting should be scored 75. Inpatients should receive a score of 999.

Understandability of speech

This score is based on the interviewer's ability to understand the patient during conversation (in this case, based on conversation about normalcy of diet and public eating). The score beside the description that best fits the patient should be chosen. The assessor should assess the clarity of speech when not directly facing the patient, or whether face-to-face contact is required to understand them.

Normalcy of Diet	Eating in public	Speech intelligibility
100 Full diet with no restrictions 90 Full diet with liquid assistance 80 All meats 70 Carrots, celery (crunchy) 60 Dry bread & crackers 50 Soft, chewable foods (pasta, canned soft fruits, fish) 40 Soft foods requiring no chewing e.g. mashed potato, apple sauce 30 Puree 20 Warm liquids 10 Cold liquids 0 Non oral	100 No restriction of place, food or companion (eats out at any opportunity) 75 No restriction of place, but restricts diet when in public (eats anywhere, but may limit intake to less "messy" foods (e.g., liquids) 50 Eats only in presence of selected persons in selected places 25 Eats only at home in presence of selected persons 0 Always eats alone	100 Always understandable 75 Understandable most of the time; occasional repetition necessary 50 Usually understandable; face-to-face 25 Never understandable; may use written 0 No communication

CRF completion

The PSS-HN assessment CRF should be completed as soon as possible after completion of the assessment.

Appendix 2: IDDSI Functional Diet Score: SOP

Purpose:
To describe the procedures employed when evaluating the IDDSI functional diet score

Scope:
This SOP outlines the procedure to be carried out by the co investigator or trained Speech and Language Therapists (SLTs), when assigning the IDDSI functional diet score.

Procedure:
Timing of assessments
The IDDSI functional diet score is to be carried out at the time points as specified in the protocol: at baseline, and at 3, 6, and 12 following diagnosis.

Assessor
The IDDSI functional diet score assessment should only be performed by appropriately trained staff a member of the research team or trained SLT.

Assessment
It is anticipated that the IDDSI functional diet assessment will take approx. 2 minutes to complete. Scores for the IDDSI functional score are determined following an unstructured interview regarding the food and drinks currently being managed by the patient. The scores range from 0 to 8 with higher scores indicating better function.

The IDDSI Functional Diet Scale score corresponds to the number in the intersecting cell of the column showing the food level and the row showing the drink level recommended for the patient. An IDDSI Functional Diet Scale score of 0 applies for recommendations of nothing by mouth (NPO), with exclusive nonoral feeding.

FOOD LEVELS						
7	6	5	4	3	N/A (no food)	
3	2	1	N/A	N/A	0	N/A (no drinks)
4	3	2	1	N/A	N/A	4
5	4	3	2	1	N/A	3
6	5	4	3	2	1	2
7	6	5	4	3	2	1
8	7	6	5	4	3	0

DRINK LEVELS

Appendix 3: 100ml Water Swallow Test (100ml WST) SOP

Purpose:
To describe the procedures employed when evaluating swallowing using the 100ml WST.

Scope:
This SOP outlines the procedure to be carried out by the co investigator or trained Speech and Language Therapists (SLTs), performing the100ml WST.

Procedure:
Timing of assessments
The 100ml WST is to be carried out at the time points as specified in the protocol: at baseline, and at 3, 6, and 12 following diagnosis.

Assessor
The 100ml WST should only be performed by a member of the research team or trained SLT

Assessment
It is anticipated that the 100ml WST assessment will take approx. 2 minutes to complete.
Patient should be alert, in an upright, comfortable position. If possible, the patient should be allowed to rest for a few minutes after arrival to gain composure.
If a patient is already using a head posture on fluids to eliminate aspiration/ penetration the WST should still be performed. This does not mean an immediate fail.
If patients are anxious about doing the test, a tester cup can be given to patients to reduce anxiety prior to the actual test. The tester cup can also be used to help patients clear any secretions from the throat before the WST is performed.
Whether a tester cup is appropriate is left to the clinical judgement of the treating SLT or the individual delegated to perform the WST.
It should also be re-emphasised that patients can take as much time as they need and they may stop the test at any time if they feel uncomfortable

The following is needed to perform the WST:

- Stopwatch
- Plastic cup
- Syringe or measuring cup
- Tap water

Face-to-face assessment:
The assessor measures 100mL of water (neither warm, nor chilled) in a plastic cup using the syringe or measuring cup.
The patient is asked to drink all the water “as quickly as possible, without making themselves uncomfortable”, and without trying to talk during the assessment.

The assessor simultaneously places their fingers gently on the patient's thyroid cartilage to measure the number of swallows. Timing starts when the water touches the patient's bottom lip and stops on the last swallow (including any breaks that might be required between swallows), including any final clearance swallow.
The WST should not be performed if individuals have been recommended by their managing clinician to remain nil by mouth.
If there are overt signs of significant aspiration (explosive coughing, prolonged coughing) or the patient is becoming distressed, the assessment and timing is stopped immediately and the remaining amount of water measured and recorded.
It is acceptable if patients cannot finish the test – inability to complete the test is an important result and should be reported on the CRF by recording how much water the patient swallowed.
It is recommended that patients who are unable to complete the WST should be highlighted to SLTs for further review as per standard care.

Remote assessment
Ahead of the assessment, ask the patient to measure 100ml of water into a clear glass.
Set the video-conferencing up, so that the patient is in full view of the camera.
Explain that you are going to time them drinking the water and count the number of swallows taken.
Demonstrate to them a lateral head position with shoulders turned (but not their neck) for the task to enable viewing. Demonstrate the position of their hand holding the glass, ensuring it is on the opposite side to the video camera to give the assessor a full view.
Give the following instructions to the patient: 'I would like you to drink all of the water as quickly and as comfortably as possible for you. I am going to count the number of swallows and time it takes for you to finish the water. Please start when you are ready. `
Using the stopwatch, the assessor times the swallow test from when the water reaches the patient's lips, to when all the water has been swallowed and there is no water remaining in the glass. The assessor simultaneously counts the number of swallows taken to swallow 100ml, by observing the upward movement of the Adam's Apple (one elevation equals one swallow). The assessor records the time taken and number of swallows to complete the water swallow test.

Recording and Reporting
The assessor records:

- The number of swallows taken
- The time taken to complete the task (in seconds; round to nearest second)
- The amount of water the patient swallowed
- The presence/absence of any signs of aspiration/ penetration (throat clear/ cough/ wet voice) during or after the task.

In the database input swallow volume (mls swallowed / number of swallows) swallow capacity (mls swallowed / time taken in seconds)
CRF completion

The 100ml WST assessment CRF should be completed as soon as possible after completion of the assessment.

Appendix 4: Dynamic Imaging Grade of Swallowing Toxicity for Fibreoptic Endoscopic Evaluation of Swallowing (FEES-DIGEST) SOP

Purpose:
To describe the procedures employed when evaluating swallowing toxicity using the FEES_ DIGEST grading system.

Scope:
This SOP outlines the procedure to be carried out by the co investigator or trained Speech and Language Therapists (SLTs) when grading the FEES- DIGEST.

Procedure:
Timing of assessments
The FEES_DIGEST is to be carried out at the time points as specified in the protocol: at baseline, and at 3, 6, and 12 following diagnosis.

Assessor
The FEES-DIGEST assessment should only be performed by a member of the research team or appropriately trained SLT.

Assessment
It is anticipated that the FEES-DIGEST will take approx. 20 minutes to complete.
The Fibreoptic Endsocopic Evaluation of Swallowing is carried out as per the guidelines in the Royal Marsden Fibreoptic Endoscopic Evaluation of Swallowing (FEES) policy 1762.

CRF completion
The FEES DIGEST CRF should be completed as soon as possible after completion of the assessment

Appendix 5: Protocol Version History

Version	Date	Reason for Change
V2.0	12.04.2022	Protocol updated to facilitate remote consent from participants both during the COVID-19 pandemic and until end of study recruitment.
V3.0	19.12.2022	Minor update to protocol wording to describe the patient population, no changes made to the eligibility criteria Named study statistician removed as not applicable
V4.0	09.02.2023	Addition of retrospective patient cohort for Part B of the study and appropriate adjustment to the sample size for the study
V5.0	28.02.2023	Addition of PIC sites as a recruitment strategy
V5.1	22.05.2024	End point data to be collected to 6 months only. Removal of adverse event reporting requirements.