Single-arm, Phase II Study Evaluating the Clinical Impact of Navigation on Delays and Racial Disparities Starting Postoperative Radiation Therapy for Adults with Locally Advanced Head and Neck Cancer: The NDURE Study

Protocol Number: CTO# 102963

National Clinical Trial (NCT) Identified Number: NCT03821064

Principal Investigator (PI): Evan Graboyes, MD

Sponsor: Hollings Cancer Center (HCC)

Grant Title: Improving the Timeliness and Equity of Adjuvant Therapy Following Surgery for Head and Neck Cancer

Grant Number: 2K12 CA157688-6

Funded by: NCI

Version Number: v.3

31 July 2019

CONFIDENTIALITY STATEMENT

This document is confidential communication. Acceptance of this document constitutes agreement by the recipient that no unpublished information contained herein will be published or disclosed without prior approval of the Principal Investigator or other participating study leadership and as consistent with the National Institutes of Health (NIH) terms of award.

SUMMARY OF KEY CHANGES FOR PROTOCOL VERSION 3		
Section Number & Title	Description of Change	Brief Rationale
5.1 Inclusion Criteria	Specified differences in staging between 7th and 8th edition of AJCC as it relates to HPV-positive and HPV-negative HNC Removal of inclusion criteria related to willingness to comply with study	Adjuvant therapy decisions for surgically-managed HPV-related HNC are based on 7th edition staging Recommendation of MUSC IRB in similar type of trial
5.2 Exclusion Criteria	Added specific adverse features that are indications for adjuvant therapy	Prevent uncertainty about eligibility
5.4 Screen Failures	Defined screen failure as subject who consents to participate in this study but is not subsequently assigned to the study intervention	Reflect change to efficacy analytic population from ITT to modified ITT (with modification to address patients who were previously described as screen failures)
9.3 Populations for Analyses	Switched from ITT to modified ITT for efficacy analyses	Facilitate analysis of expected patients who enroll into study but over time develop exclusion criteria (and thus analysis for efficacy)

Table of Contents

STATEMENT OF COMPLIANCE 6
INVESTIGATOR'S SIGNATURE 7
1 PROTOCOL SUMMARY 8
1.1 Synopsis 8
1.2 Schema 11
1.3 Schedule of Activities 12
2 INTRODUCTION 12
2.1 Study Rationale 12
2.2 Background 13
2.3 Risk/Benefit Assessment 14
2.3.1 Known Potential Risks 14
2.3.2 Known Potential Benefits 14
2.3.3 Assessment of Potential Risks and Benefits 14
3 OBJECTIVES AND ENDPOINTS 15
4 STUDY DESIGN 16
4.1 Overall Design 16
4.2 Scientific Rationale for Study Design 16
4.3 Justification for Intervention 16
4.4 End-of-Study Definition 17
5 STUDY POPULATION 17
5.1 Inclusion Criteria 17
5.2 Exclusion Criteria 17
5.3 Lifestyle Considerations 18
5.4 Screen Failures 18
5.5 Strategies for Recruitment and Retention 18
6 STUDY INTERVENTION(S) OR EXPERIMENTAL MANIPULATION(S) 19
6.1 Study Intervention(s) or Experimental Manipulation(s) Administration 19
6.1.1 Study Intervention or Experimental Manipulation Description 20
6.1.2 Administration and/or Dosing 21
6.2 Fidelity 21
6.2.1 Interventionist Training and Tracking 21
6.3 Measures to Minimize Bias: Randomization and Blinding 21
6.4 Study Intervention/Experimental Manipulation Adherence 21
6.5 Concomitant Therapy 21
6.5.1 Rescue Therapy 21
7 STUDY INTERVENTION/EXPERIMENTAL MANIPULATION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL 21
7.1 Discontinuation of Study Intervention/Experimental Manipulation 21
7.2 Participant Discontinuation/Withdrawal from the Study 21
7.3 Lost to Follow-Up 22
8 STUDY ASSESSMENTS AND PROCEDURES 22
8.1 Endpoint and Other Non-Safety Assessments 22

9 STATISTICAL CONSIDERATIONS 25
9.1 Statistical Hypotheses 25
9.2 Sample Size Determination 25
9.3 Populations for Analyses 26
9.4 Statistical Analyses 27
9.4.1 General Approach 27
9.4.2 Analysis of the Primary Endpoint(s) 27
9.4.3 Analysis of the Secondary Endpoint(s) 28
9.4.4 Safety Analyses 28
9.4.5 Baseline Descriptive Statistics 28
9.4.6 Planned Interim Analyses 28
9.4.7 Sub-Group Analyses 29
9.4.8 Tabulation of Individual Participant Data 29
9.4.9 Exploratory Analyses 29
10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS 29
10.1 Regulatory, Ethical, and Study Oversight Considerations 29
10.1.1 Informed Consent Process 29
10.1.2 Study Discontinuation and Closure 29
10.1.3 Confidentiality and Privacy 30
10.1.4 Future Use of Stored Specimens and Data 30
10.1.5 Key Roles and Study Governance 30
10.1.6 Safety Oversight 30
10.1.7 Clinical Monitoring 30
10.1.8 Quality Assurance and Quality Control 30
10.1.9 Data Handling and Record Keeping 31
10.1.11 Publication and Data Sharing Policy 31
10.2 Additional Considerations 32
10.3 Abbreviations and Special Terms 32
10.4 Protocol Amendment History 34
11 REFERENCES 33

STATEMENT OF COMPLIANCE

The trial will be conducted in accordance with International Council on Harmonisation Good Clinical Practice (ICH GCP), applicable United States (US) Code of Federal Regulations (CFR), and the National Cancer Institute (NCI) Terms and Conditions of Award. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the funding agency and documented approval from the Institutional Review Board (IRB), and the Investigational New Drug (IND) or Investigational Device Exemption (IDE) sponsor, if applicable, except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form(s) must be obtained before any participant is consented. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form(s) will be IRB approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

INVESTIGATOR'S SIGNATURE

The signature below constitutes the approval of this protocol and provides the necessary assurances that this study will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations and ICH guidelines, as described in the *Statement of Compliance* above.

Principal Investigator:

Signed:  Date: 7/31/19

Name: Evan Graboyes

Title: Single-arm, Phase II Study Evaluating the Clinical Impact of Navigation on Delays and Racial Disparities Starting Postoperative Radiation Therapy for Adults with Locally Advanced Head and Neck Cancer: The NDURE Study

Investigator Contact Information
Affiliation: Medical University of South Carolina
Address: 135 Rutledge Avenue, MSC 550, Charleston, SC 29425
Telephone: (843)-792-0719
Email: graboyes@musc.edu

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

•

Title: Single-arm, Phase II Study Evaluating the Clinical Impact of Navigation on Delays and Racial Disparities Starting Postoperative Radiation Therapy for Adults with Locally Advanced Head and Neck Cancer: The NDURE Study

Grant Number: 2K12CA157688-6

Study Description: In this study, we evaluate the feasibility, acceptability, preliminary clinical impact, and preliminary behavioral impact of NDURE (Navigation for Disparities and Untimely Radiation thErapy), our multi-level, theory-based navigation intervention to improve timely, equitable post-operative radiation treatment (PORT) among Head and Neck Cancer (HNC) patients. We hypothesize that NDURE will be feasible, acceptable, improve the timeliness of PORT for white and African American (AA) HNC patients and decrease disparities in delay between the two groups by improving system-, interpersonal-, and individual-level health behavior constructs.

Objectives:

Primary Objective:
1. To evaluate the preliminary clinical impact of NDURE on delays starting PORT among white and AA HNC patients.

Secondary Objectives:
1. To evaluate the preliminary clinical impact of NDURE on racial disparities in delays starting PORT among white and AA HNC patients.

2. To compare the rate of PORT delay in NDURE to local and national historical controls.

3. To evaluate the preliminary clinical impact of NDURE on barriers and cancer care delivery processes.

3. To assess the feasibility of NDURE among white and AA HNC patients.

4. To assess the acceptability of NDURE to white and AA HNC patients and HNC providers.

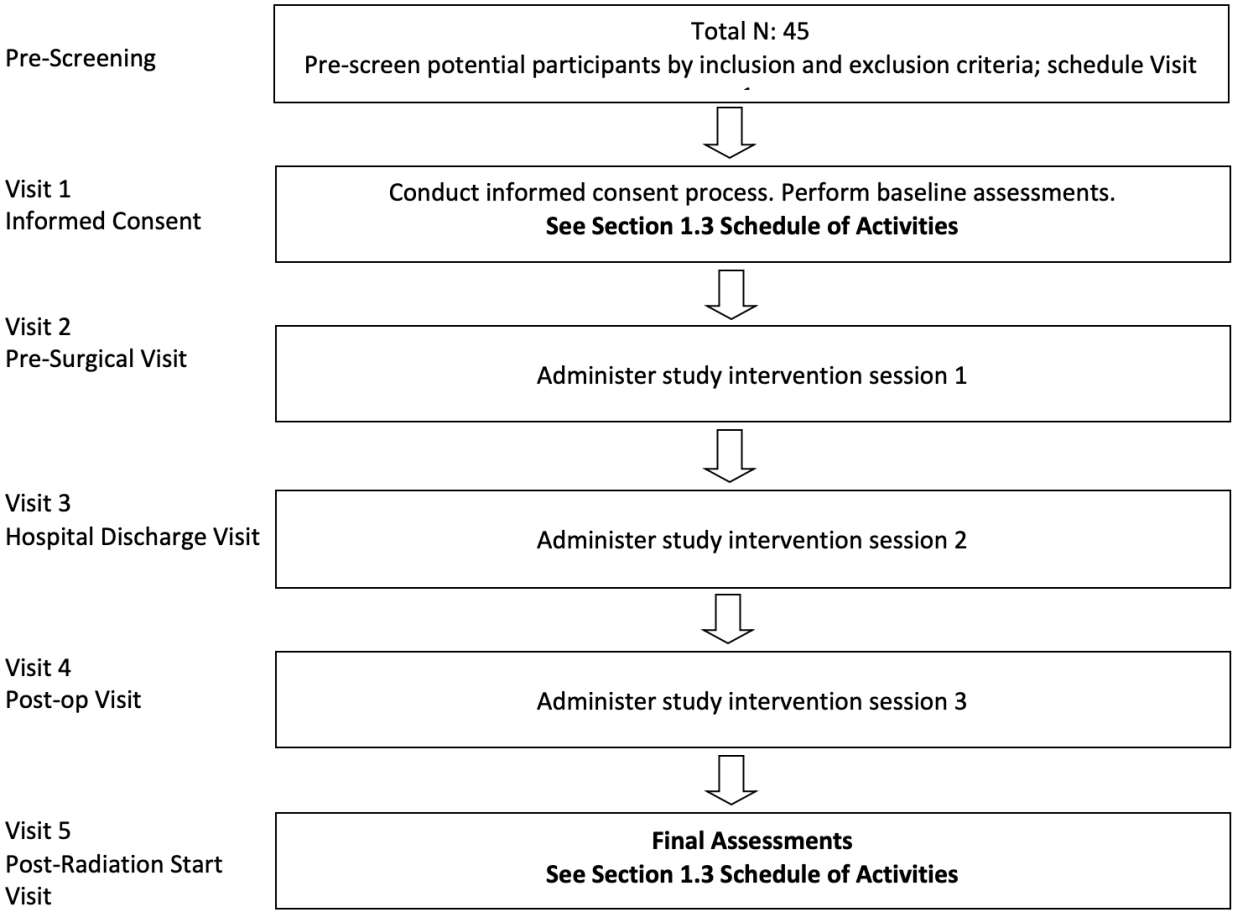
5. To evaluate the preliminary behavioral mechanism of action of NDURE.

Endpoints:	Primary Endpoint: Initiation of postoperative PORT > 6 weeks after surgery Secondary Endpoints: Racial disparities in initiation of PORT > 6 weeks after surgery Days between surgery and the start of PORT Barriers resolved Unresolved barriers Pre-Surgical Radiation Consultation Pre-Radiation Therapy Dental Extractions Surgery to Pathology Report $\leq$ 7 days Surgery to PORT Referral $\leq$ 10 days RT Referral to Consult $\leq$ 10 days RT Consult to Initiation $\leq$ 21 days NDURE Accrual NDURE Completion Navigation Session Completion Navigator Caseload Navigator Time Allocation (Direct) Navigator Time Allocation (Indirect) Patient Satisfaction with the Interpersonal Relationship with the Navigator Score Patient Satisfaction with Logistical Aspects of Navigation Scale Score Care Transition Measure-15 (CTM-15) Score Δ Interpersonal Support Evaluation List-12 (ISEL-12) Score Δ Perceived Susceptibility Score Δ Illness Perception Questionnaire-Revised (IPQ-R) Consequences Sub-Scale Score Δ Perceived Barriers Score Δ Communication & Attitudinal Self-Efficacy Scale (CASE)-Cancer Score
Study Population:	The study population will consist of patients 18 years of age or older, self-identified white or AA race, locally advanced HNC (American Joint Committee on Cancer [AJCC] clinical stage III-IV) undergoing curative intent surgery at the Medical University of South Carolina (MUSC) followed by PORT (at MUSC or non-MUSC).
Phase or Stage:	II
Description of Sites/Facilities Enrolling Participants:	The study will be conducted, and participants enrolled, at the MUSC Hollings Cancer Center (HCC) Head and Neck Tumor Center. The Head and Neck Tumor Center is a high-volume, multidisciplinary center designed for unsurpassed clinical care and optimized for integration of research activities. The Head and Neck Tumor Center is a regional center of excellence for HNC clinical care.

Description of Study Intervention/Experimental Manipulation:	NDURE is a theory-based, multi-level patient navigation (PN) intervention consisting of three in-person, clinic-based sessions of manualized PN with multiple intervention components that target system- (care coordination), interpersonal- (social support), and individual- (health belief model (HBM); perceived susceptibility, severity, barriers, self-efficacy) level health behavior theoretical constructs to reduce barriers to care, increase HNC care delivery, and improve clinical outcomes (timely, equitable PORT). NDURE will be delivered from surgical consultation to PORT initiation (~3 months). The three in-person NDURE navigation sessions, which are expected to take 30-60 minutes each, will coincide with the presurgical consult, hospital discharge, and 1st postoperative clinic visit, time points chosen to facilitate case identification and coordination across key care transitions.
Study Duration:	18 months
Participant Duration:	5 months

1.2 SCHEMA

Flow Diagram



1.3 SCHEDULE OF ACTIVITIES (SOA)

	Pre-screening (Pre-consent)	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5
Electronic Medical Record (EMR) Review Eligibility	X					
Informed Consent		X				
Demographics		X				
Clinical and oncologic history		X				
Cultural Factors		X				
Barrier Load		X	X	X	X	X
Symptom Severity		X	X	X	X	X
Outcome Evaluation						
Barrier Reduction			X	X	X	X
Unresolved Barriers			X	X	X	X
Satisfaction with Navigation-Interpersonal						X
Satisfaction with Navigation-Logistical						X
Care Transition						X
Interpersonal Support		X				X
Perceived Susceptibility		X				X
Perceived Consequences		X				X
Perceived Barriers		X				X
Perceived Self-Efficacy in Cancer Care		X				X

2 INTRODUCTION

2.1 STUDY RATIONALE

HNC is responsible for 14,000 deaths annually in the US and has poor survival (50% at 5 years) despite intense treatment including surgery, radiation, and chemotherapy[1]. HNC is also a disease with significant racial disparities in mortality; AAs have a 51% relative decrease in survival compared to whites[2]. Delays starting PORT after HNC surgery are a key driver of high mortality for all HNC patients and racial disparities in survival for AAs. As such, the delivery of timely PORT is an appealing therapeutic target to address both issues[3,4]. We have shown that delayed, non-guideline-adherent PORT initiation (> 6 weeks after surgery[5]) affects 56% of HNC patients[6], is 31% more common in AA HNC patients than whites[6], is associated with an 11% absolute decrease in 5-year survival[7], and is a key driver of racial differences in mortality[3]. Our pilot qualitative data suggest that treatment toxicity, travel distance, care coordination, finances, support, knowledge, and communication are barriers to timely, equitable PORT. Delivering timely PORT to all HNC patients is critical to prevent excess mortality and racial disparities in survival. Unfortunately, effective interventions to decrease delays and racial disparities starting PORT are unknown[8,9], due in part to the lack of understanding of the relevant barriers in this clinical setting. One potential strategy to improve timely, equitable PORT is patient navigation (PN), a barrier-focused intervention that improves the timeliness and racial equity of initial cancer care (screening, treatment initiation)[10,11]. However, the impact of PN on delays and racial disparities starting PORT, a different point on the cancer care continuum than screening and treatment initiation, is unknown[12]. In this proposal, we extend our work to develop and evaluate the

feasibility, acceptability, and preliminary clinical impact of NDURE, our multi-level, theory-based PN intervention to improve timely, equitable PORT among HNC patients.

2.2 BACKGROUND

Head and Neck Cancer (HNC) is a Disease with High Mortality and Racial Disparities in Survival. HNC, which affects the tongue, pharynx, larynx, and neck, is diagnosed in 65,000 patients in the US annually and causes 14,000 deaths per year[1]. No screening tests exist for HNC, and as a result, more than two-thirds of patients present with locally advanced disease[1]. Despite aggressive multimodal therapy consisting of surgery followed by postoperative radiation therapy (PORT) and concurrent chemotherapy[5], outcomes remain poor with only 50% of patients with locally-advanced HNC surviving 5 years[1]. HNC is also a disease with significant racial disparities in mortality; African Americans (AAs) with HNC have a 19% absolute decrease in 5-year survival relative to white HNC patients[13] and a 51% relative decrease in survival[2].

Delays Starting PORT Contribute to High Mortality in HNC and Racial Disparities in Survival. Delays in cancer care delivery are a key driver of mortality for HNC patients[14] and a source of racial disparities in survival for AAs[3]. The critical time period for HNC patients is the time from surgery to the start of PORT[8,15], the only aspect of timely HNC care incorporated in National Comprehensive Cancer Network Guidelines ($\leq$ 6 weeks after surgery)[5]. Delays starting PORT are associated with increased recurrence and decreased survival[7,16,17]. The 11% improved 5-year survival seen with timely PORT[7] is large, comparable in magnitude to the benefit seen from adding Cisplatin to PORT in landmark HNC trials[18,19]. Unfortunately, delays starting PORT affect 56% of HNC patients[6]. Delays starting PORT also disproportionately affect AAs, who are 31% more likely to experience delays than whites after adjusting for insurance, income, education, and stage[6]. The high rate of delayed PORT among AA HNC patients is a source of preventable mortality and contributes to racial disparities in survival[7].

The Barriers that Contribute to Delays and Racial Disparities Starting PORT After HNC Surgery are Unknown. AA race, insurance status, prolonged travel distance, and care fragmentation are associated with delayed PORT[6,20-22]. However, the barriers to timely care delivery at the patient-, provider-, and system-level remain unknown. As a result, the development of targeted, multi-level interventions to address barriers and improve the delivery of timely, equitable PORT for HNC patients has been impeded. To prevent continued treatment delays, it is critically important to identify the barriers to delivering timely, equitable PORT.

Effective Interventions to Decrease Delays and Racial Disparities Starting PORT are Lacking. The care delivery pathway for PORT, which is potentially modifiable through a multi-level intervention, represents an appealing target to decrease mortality and racial disparities in survival for HNC patients[3,4,8]. Unfortunately, despite the large clinical impact of delayed PORT on mortality and racial disparities in survival, no effective interventions have been described[8,9,23]. A prior study using an atheoretical, provider-centric approach did not find a decrease in the rate of PORT delay[24]. Improving the timeliness of PORT for white and AA HNC patients is crucial to improving survival for all HNC patients and decreasing racial disparities in mortality.

Patient Navigation (PN) is a Promising Strategy to Deliver Timely, Equitable PORT after HNC Surgery. PN is a patient-centered intervention that addresses barriers to cancer care, thereby improving the delivery of timely, equitable cancer screening, decreasing racial differences in post-screening diagnostic resolution, and decreasing care fragmentation[10,11,25-27]. However, the efficacy of PN in the sequential multimodal cancer care setting (e.g. surgery then PORT) is unknown[12]; care transitions following surgery involve unique care barriers and care coordination challenges[28]. To address the lack of effective interventions to decrease delays and racial disparities starting PORT after HNC surgery[8], we will develop and test NDURE (Navigation for Disparities and Untimely Radiation thErapy), our multi-level, theory-based PN intervention to improve timely, equitable PORT among HNC patients. The underlying scientific premise is that our NDURE PN intervention has the potential to decrease delays starting PORT among HNC patients because PN is most effective in 1) populations with low adherence rates[10] (timely PORT adherence is < 50% overall and <40% among AAs[6]); 2) racial minority populations[10,29] (delays starting PORT are 31% more common in AAs[6]); and 3) the setting of fragmented care[10,27]

(PORT delivery involves coordinating consults with seven medical specialties[23], care transitions from inpatient to outpatient, and care transitions across healthcare systems [in 51% of cases[6]]).

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

Overall, this research study poses no more than minimal risks to participants. There are no physical, financial, legal, social, or cultural, risks to the study participants by joining this study. There are slight psychological risks, as described below. There is a slight risk that subjects may experience adverse psychological reactions such as anxiety or stress as a result of discussing issues related to cancer or barriers to cancer care. We believe that this risk is minimal. We are using survey items that are commonly used in clinical settings and subjects are likely to have had prior exposure to similar types of questions as part of their medical care. Furthermore, in our past studies with white and AA men and women with HNC, the overwhelming majority of respondents have said they found the questions that we have asked related to care have not been upsetting.

There is also a slight risk that confidential information about the participant may be accidentally disclosed as study participants may be asked to provide information considered confidential or private during study interviews. The likelihood of this risk is low as all the investigators have been involved in similar research in the past and have not experienced this problem before due to adequate safeguards.

The decision to participate in this research will be voluntary and individuals may refuse to take part or choose to stop taking part at any time. Participants will also be encouraged to take their time when answering questions and may decline to answer any question at any time. If patients become upset talking about their cancer and the barriers that they faced, they will be offered a referral to the HCC Behavioral Medicine program (which is covered by most health insurance programs) or the HCC Social Worker who will offer links to other HCC and community resources.

2.3.2 KNOWN POTENTIAL BENEFITS

Extrapolating from data about PN in other settings, NDURE may improve the timeliness of PORT after HNC surgery and decrease racial disparities in timely HNC care. However, although we hypothesize a direct benefit to participants in the NDURE study (in terms of timely HNC care), it is unknown whether patients will experience a direct benefit. Data generated from this study are expected to provide benefits to society by providing new knowledge about a practical and scalable strategy for addressing racial disparities in the timeliness of PORT in HNC patients. Because timely PORT is associated with decreased rates of recurrence and improved survival, it is expected that if we decrease racial disparities in delays starting PORT, we will improve survival and racial equity in outcomes.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

The decision to participate in this research will be voluntary. Participants will be informed that they can stop participating at any time and/or refrain from answering any questions that make them uncomfortable. The interviewers are trained researchers with experience conducting interviews related to cancer. By using survey items that are commonly used in clinical settings (to which subjects have likely had prior exposure as part of their medical care) we will minimize psychological risk. If a participant has a psychological adverse event (AE) talking about his/her cancer and/or the barriers that he/she faced during treatment, the participant will be offered a referral to the HCC Behavioral Medicine program (which is covered by most health insurance programs) or the HCC Social Worker who will offer links to other HCC and community resources as detailed in the Data and Safety Monitoring Plan. Immediate backup and support will be available.

To help ensure and protect privacy of participants and confidentiality of research data for the study, we will assign a unique study ID number to each subject's information in place of his/her name and will label data collection forms with the ID number. All hard copy and electronic files will be stored appropriately using double-locked methods and password-protection. Only the study team members will have access to study records. Participant data will be collected

and recorded on either a password-protected electronic data capture format (REDCap) or paper-based forms depending upon patient preference. For the paper collection data method, the data collection form will be labeled only with the participant's unique study ID number, and then stored within locked drawers in a locked office.

The information on these paper forms will be transferred to a password-protected REDCap database. Any exported data for analysis will be de-identified with all privately identifiable information automatically removed. The key linking subject ID number to an individual will be stored in the password protected REDCap database. The audio recordings from the qualitative interviews will be labeled only with the patient's unique study ID and stored using password-protected files only accessible by the study team through password-protected servers. Once data have been collected, only de-identified data will be exported for analysis. All study personnel will participate in training on protecting the privacy of study participants and personal information will not be disclosed to anyone outside of the research team. Only the principal investigator and study staff participating in data collection or analysis will have access to the data. We have no plan to use laptops, jump drives, CDs/DVDs to transport data.

On the whole, given the minimal risks to the study participants and the potential benefit of the research to participants and society, we believe that the potential reward to participants and society substantially outweighs the risks to the participants.

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS
Primary	
To evaluate the preliminary clinical impact of NDURE on delays starting PORT among white and AA HNC patients.	Initiation of PORT > 6 weeks after surgery
Secondary	
To evaluate the preliminary clinical impact of NDURE on racial disparities in delays starting PORT among white and AA HNC patients.	Initiation of PORT > 6 weeks after surgery
	Days between surgery and the start of PORT
To compare the rate of PORT delay in NDURE to local and national historical controls.	Initiation of PORT > 6 weeks after surgery
	Days between surgery and the start of PORT
To evaluate the preliminary clinical impact of NDURE on barriers and cancer care delivery processes.	Barriers resolved
	Unresolved barriers
	Pre-surgical Radiation Consultation
	Pre-RT Dental Extractions
	Surgery to Pathology Report $\leq$ 7 d
	Surgery to PORT Referral $\leq$ 10 d
	RT Referral to Consult $\leq$ 10 d
	RT Consult to Initiation $\leq$ 21 d
To assess the feasibility of NDURE among white and AA HNC patients.	NDURE Accrual
	NDURE Completion
	Navigation Session Completion
	Navigator Caseload
	Navigator Time Allocation (Direct)
	Navigator Time Allocation (Indirect)
To assess the acceptability of NDURE to white and AA HNC patients and HNC providers.	Patient Satisfaction with the Interpersonal Relationship with the Navigator Score
	Patient Satisfaction with Logistical Aspects of Navigation Scale Score

OBJECTIVES	ENDPOINTS
To evaluate the preliminary behavioral mechanism of action of NDURE	Care Transition Measure-15 (CTM-15) Score
	Δ Interpersonal Support Evaluation List-12 Score
	Δ Perceived Susceptibility Score
	Δ Illness Perception Questionnaire-Revised (IPQ-R) Consequences Sub-Scale Score
	Δ Perceived Barriers Score
	Δ Communication & Attitudinal Self-Efficacy Scale (CASE)-Cancer score

4 STUDY DESIGN

4.1 OVERALL DESIGN

We will conduct a single-site, single-arm phase II clinical trial of NDURE among HNC patients undergoing surgery and PORT (n=45; AA n=15; white n=30). NDURE is a theory-based, multi-level PN intervention consisting of three in-person, clinic-based sessions of manualized PN with multiple intervention components that target system- (care coordination), interpersonal- (social support), and individual- (HBM; perceived susceptibility, severity, barriers, self-efficacy) level health behavior theoretical constructs to reduce barriers to care, increase HNC care delivery, and improve clinical outcomes (timely, equitable PORT). NDURE will be delivered from surgical consultation to PORT initiation (~3 months). The three in-person NDURE navigation sessions, which are expected to take 30-60 minutes each, will coincide with the presurgical consult, hospital discharge, and 1st postoperative clinic visit, time points chosen to facilitate case identification and coordination across key care transitions. Measures of PORT delay will be analyzed overall (primary outcome) and for racial differences (secondary outcome). Measures of the preliminary clinical impact of NDURE on PORT barrier reduction and delivery of key HNC care processes will be collected (secondary outcome), feasibility (secondary outcome; accrual rate, NDURE completion rate, PN caseload), acceptability (secondary outcome; satisfaction with PN). Measures of the theoretical constructs underlying the multi-level, theory-based NDURE intervention will be compared pre- and post-intervention. Post-intervention qualitative work with patients and providers will help refine NDURE.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

We favor the single-arm design over a single-site randomized control trial (RCT) for the following reasons. First, randomizing patients to NDURE vs standard of care within a single site would contaminate the 'control' group due to unmeasured, off-target effects of NDURE on processes of care PI and culture, thereby producing an underestimation of NDURE's true impact. Second, statistical models have shown that a single-arm design is preferred to a two-arm design for phase II trials in situations such as ours when the historical controls are well defined and the sample size is small[30]. Third, our design was chosen not to determine clinical efficacy, but rather to provide preliminary estimates of clinical impact (as determined by the point estimates of rate of PORT delay relative to historical controls) and precision (margin of error) to design a larger scale multi-site cluster-randomized clinical trial to test the efficacy of NDURE[31]. Consistent with this study design is our limited sample size and the recognition that our exploratory, early phase trial will not produce definitive clinical conclusions[32].

4.3 JUSTIFICATION FOR INTERVENTION

The three in-person NDURE sessions, which are expected to take 30-60 minutes each, will coincide with the presurgical consult, hospital discharge, and 1st postoperative clinic visit, time points chosen to facilitate case identification and coordination across key care transitions. These timepoints also promote the feasibility of NDURE delivery as nearly 100% of patients attend these three visits (despite travel distance-related barriers[33]) since patients 1) cannot have surgery without their presurgical consult; 2) are hospitalized postoperatively; and 3) return for the 1st postoperative visit for drain/tube removal.

4.4 END-OF-STUDY DEFINITION

A participant is considered to have completed the study if he or she has completed the baseline assessment, at least two NDURE intervention sessions, and the final follow-up assessment.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

Patient and disease characteristics

1. Age > 18 years at the time of screening
2. Histologically or pathologically confirmed invasive SCC (or histologic variant) of the oral cavity, oropharynx (p16 positive, negative, or unknown), hypopharynx, larynx, unknown primary, paranasal sinuses, or nasal cavity.
    a. In situations in which the patient fulfills all other inclusion criteria but the biopsy shows SCC in-situ or moderate/severe dysplasia (without definitive evidence of invasive SCC), but the patient is scheduled to undergo curative intent surgery by the treating oncologic surgeon due to clinical suspicion of invasive SCC, the diagnosis of SCC-in situ or moderate/severe dysplasia is sufficient to full the pathologic diagnosis enrollment criterion.
3. American Joint Committee on Cancer (AJCC) clinical stage grouping III-IV (8th edition) for patients with SCC of the oral cavity, p16-negative oropharynx, hypopharynx, larynx, paranasal sinuses, and nasal cavity; or AJCC clinical stage grouping III-IV (7th edition) for patients with p16-positive SCC of the oropharynx or unknown primary.
    a. At screening, AJCC clinical stage grouping should be determined based on a combination of physical exam, diagnostic evaluation with cross sectional imaging of the neck (computerized tomography (CT) and/or magnetic resonance imaging (MRI)) and/or 18-F-fluoro-deoxyglucose positron emission tomography (FDG PET) CT within 30 days
    b. In situations in which the patient fulfills all other inclusion criteria but the biopsy shows SCC in-situ or moderate/severe dysplasia (without definitive evidence of invasive SCC), but would otherwise have an appropriate clinical stage grouping as defined in criterion 5, the diagnosis of SCC-in situ or moderate/severe dysplasia is sufficient to full the staging enrollment criterion.
4. No prior exposure to radiation therapy, with or without concurrent chemotherapy, for treatment of HNSCC in the definitive or adjuvant therapy settings

Surgery and adjuvant therapy eligibility

5. Plan for curative intent surgery at MUSC
    a. At screening, plan for curative intent surgical resection of the HNSCC at MUSC must be deemed likely by the treating surgeon and/or multidisciplinary tumor board, which must include a fellowship-trained head and neck oncologic surgeon
6. Plan for PORT (at MUSC or non-MUSC) with or without concurrent chemotherapy following curative intent surgery
    a. At screening, plan for adjuvant therapy following curative intent surgical resection of the HNSCC at MUSC must be deemed likely by the treating surgeon and/or multidisciplinary tumor board, which must include a fellowship-trained head and neck oncologic surgeon, based on the clinical expectation of at least one of the following adverse features on final pathologic evaluation: extranodal extension (ENE), pT3 or pT4 primary, N2 or N3 nodal disease, nodal disease in levels IV or V, perineural invasion (PNI), or lymphovascular invasion (LVI)

5.2 EXCLUSION CRITERIA

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Self-identified Hispanic ethnicity
2. Presence of cognitive impairment that precludes participation
3. Neoadjuvant immunotherapy or chemotherapy
4. Failure to undergo curative intent surgery at MUSC
5. Lack of indication for PORT (with or without concurrent chemotherapy) per National Comprehensive Cancer Network (NCCN) Guidelines based on the presence of at least one of the following adverse features on final pathologic evaluation: ENE, positive margin, pT3 or pT4 primary, N2 or N3 nodal disease, nodal disease in levels IV or V, PNI, or LVI

Individuals across the lifespan will be included with the following exception: children (i.e., individuals under age 18) will be excluded. Children are not eligible to participate in the study for the following scientific reasons: 1) HNSCC is a rare pediatric malignancy; and 2) the care delivery experiences of children with HNSCC are likely very different from those of adults. The age distribution included in the study (all ages >/= 18) will allow us to evaluate the feasibility and acceptability of NDURE in individuals of across the lifespan.

Patients of non-white, non-AA racial groups (e.g. Asian American, Native American) will be excluded from the clinical trial of NDURE. Our decision to focus only on white and AA patients (and exclude other racial groups) is justified by the following considerations: 1) In terms of timely PORT, the racial disparities are largest among white compared to AA HNSCC patients (nationally and at MUSC); 2) The barriers causing racial differences in time to PORT among AAs and other racial groups may be different, necessitating a different patient navigation intervention; 3) Other non-white, non-AA racial groups make up only 1% of HNSCC patients treated at MUSC. As a result, finding a sufficient number of patients who are non-AA racial minorities to participate in the RCT of NDURE would be challenging. Patients who self-identify as being of Hispanic ethnicity will be excluded from the clinical trial of NDURE. Although Hispanic ethnicity is a risk factor for delayed PORT, we justify our exclusion of Hispanic patients from the clinical trial for the following reasons: 1) The barriers causing racial differences in time to PORT among AAs and Hispanics are likely different (e.g. language); 2) Hispanic HNSCC patients account for only 3% of patients at MUSC. As a result, finding a sufficient number of Hispanic patients to participate in the clinical trial of NDURE would be challenging.

5.3 LIFESTYLE CONSIDERATIONS

N/A

5.4 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in this study but are not subsequently assigned to the study intervention or entered in the study. Individuals who do not meet the criteria for participation in this trial (screen failure) because of meeting one or more exclusion criteria will not be rescreened.

5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

Recruitment for the single-site, single-arm, pilot trial of NDURE will occur using a clinic-based approach from the MUSC Head and Neck Tumor Center, a high-volume academic HNC program at the NCI-designated Hollings Cancer Center. Research staff will use cancer center registry data, discussion with the HNC clinical team, and the electronic medical record (EMR) to identify patients who meet study inclusion criteria. Research staff will then review clinic rosters to identify eligible patients who are scheduled for an appointment in the Head and Neck Tumor Center. Study recruitment will be facilitated through the use of tested, structured protocols. Chanita Hughes-Halbert, PhD has evidenced-based strategies that have been successfully employed to recruit AA cancer patients to therapeutic trials. We will also use structured protocols from the principal investigator (Evan Graboyes, MD) and co-mentor Katherine Sterba, PhD, MPH. These protocols have been successfully employed and refined for clinic-based recruitment of patients with HNC to

participate in behavioral research during treatment periods. Recruitment is expected to be enhanced by the active clinical practice of the PI.

Prior to studying the NDURE intervention in a clinical trial, we will pre-test our intervention in n=3 patients to ensure proper implementation into clinical workflow. These patients will participate in the intervention and outcome assessment only for the purposes of pre-testing and assessing our implementation into clinical workflow but not for the purposes of analysis towards any of the study endpoints.

We propose to accrue 45 patients (white, n=30 and AA, n=15) to the study over 13 months. Based on data from MUSC/HCC for 2018, it is expected that 125 patients/year will be eligible for the study, of whom 28 (22%) are expected to be AA and 97 (78%) are expected to be white. Based on the PI and study team's prior experience recruiting and enrolling for similar studies embedded into clinical care, we anticipate that 50% of eligible patients will accrue to this study. Based on this 50% accrual rate, over the course of 13 months, we would expect to accrue 68 patients (n=15 AAs; n=53 white). Thus, by conservative estimates with appropriate over-sampling of AAs, our overall accrual target (n=45) and for the AA racial subgroup (n=15) appear highly feasible in the allocated 13 month accrual period.

Because we plan to enroll consecutive patients for this clinic-based intervention, one potential concern relates to systematic, non-random differences between patients who participate in NDURE and patients who decline to participate. Enthusiastic, health-motivated patients may enroll while marginalized, burdened patients who distrust the medical system may preferentially decline. Alternatively, patients with few/no perceived barriers may disproportionately decline the intervention due to perceived lack of need while burdened patients participate because of the perceived need. Whichever, if any, situation occurs, our approach ensure that we will still be well positioned because we will collect information about which patients enroll/decline and their reasons for enrolling/declining to help refine NDURE for future dissemination.

Three strategies will be used to ensure retention of enrolled patients in the study. First, supportive and frequent interactions between the participant and navigator are expected to occur throughout NDURE, which should help mitigate against retention problems (for those in the NDURE arm). Second, we have accounted for the burden of surveys/questionnaires while patients are on treatment to ensure that the expected time commitment from surveys is reasonable and that the study interactions will be scheduled at a convenient time for patients (usually while at MUSC for clinical care already). Finally, remuneration will also occur on a schedule that is weighted towards providing the majority of the compensation at the end of the study time period.

Retention of subjects is not expected to be problematic since NDURE is embedded into clinical care and patients will be actively on treatment during the study. The scheduled timepoints of navigator-participant interaction (initial surgical consultation, prior to hospital discharge, first clinic visit after hospital discharge) were chosen because these are situations in which the likelihood of contact is ~100%. Although challenges with retention for cancer studies due to mortality (overall and disease-specific) and treatment toxicity are potentially problematic, we do not think that they will limit retention in this feasibility study of NDURE. The rate of on-treatment mortality (during surgery or adjuvant therapy) is quite low (<5%) and the study follow-up does not extend past the completion of therapy. Thus, lack of retention due to mortality is not expected to be significant. Treatment toxicity is potentially a problem, as patients may not want to answer surveys while undergoing treatment or choose to withdraw due to competing treatment demands. We do not expect this to be a problem, however, because NDURE will be integrated into routine clinical care and thus should not create an excess time burden for patients. In fact, it is likely that participation in the intervention, which is expected to improve care coordination and decrease barriers to care, will make this potential source of dropout less likely than other intervention trials. Using NDURE to address individualized barriers to timely HNC treatment is a significant strength and innovation of the study and will likely also improve retention relative to historical rates.

6 STUDY INTERVENTION(S) OR EXPERIMENTAL MANIPULATION(S)

6.1 STUDY INTERVENTION(S) OR EXPERIMENTAL MANIPULATION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION OR EXPERIMENTAL MANIPULATION DESCRIPTION

NDURE is a theory-based, multi-level PN intervention consisting of three in-person, clinic-based sessions of manualized PN with multiple intervention components that target system- (care coordination), interpersonal- (social support), and individual- (HBM; perceived susceptibility, severity, barriers, self-efficacy) level health behavior theoretical constructs to reduce barriers to care, increase HNC care delivery, and improve clinical outcomes (timely, equitable PORT). The NDURE intervention components and targeted theoretical constructs are outlined in **Table 1**. NDURE will be delivered from surgical consultation to PORT initiation (~3 months). The three in-person NDURE navigation sessions, which are expected to take 30-60 minutes each, will coincide with the presurgical consult, hospital discharge, and 1st postoperative clinic visit, time points chosen to facilitate case identification and coordination across key care transitions. Contact beyond the three prescribed in-person sessions will occur with a frequency and modality (e.g. text message, email, etc.) dictated by patient and navigator need. During the first in-person session, the navigator will 1) elicit barriers and facilitators to timely PORT from the patient, caregiver, and provider, 2) develop the personalized barrier reduction plan (BRP), review it with the patient, caregiver, and provider, and 3) implement the BRP. At the two subsequent in-person sessions, the navigator will review and update the BRP in an iterative, dynamic fashion, identifying new barriers and systematically tracking resolution of prior barriers until the start of PORT. The Navigator Manual provides a structured resource to guide intervention delivery and enhance reproducibility. The Patient Guide is 1) literacy-level appropriate, 2) personalized for each patient's care pathway and BRP, 3) updated longitudinally as the patient progresses along the cancer continuum, and 4) available to patients in print and/or electronically via the patient portal in the EMR.

Table 1. NDURE Intervention Components

Component	Description	Theoretical Target
Clinical Tool		
NDURE Navigation Sessions	Three manualized sessions in which the navigator develops and enacts a personalized BRP. While performing the BRP, the navigator will facilitate care coordination, link patients to resources and instrumentally assist with barrier mediation, educate patients on the risk and health consequences of PORT delay, and provide verbal reinforcement and demonstration to enhance patients' self-confidence to achieve timely PORT	-Care coordination -Instrumental support -Informational support -Perceived susceptibility -Perceived severity -Perceived barriers -Perceived self-efficacy
NDURE Navigator Manual	-Contact information for HNC providers in SC -Taxonomy of barriers to timely PORT -Resource library matched to key barriers	-Care coordination -Perceived barriers -Support
NDURE Patient Guide	-Personalized contact information for HNC team -Resources to address barriers in BRP -Personalized PORT Timeline -At-risk population and tailored risk of PORT delay -Health consequences of delayed PORT -Personalized BRP	-Care coordination -Instrumental support -Informational support -Perceived susceptibility -Perceived severity -Perceived barriers
System Changes		
Documentation	Structured EMR flowchart to document barriers and BRP that is accessible to HNC care team	Care coordination
Conferences	Multi-D weekly review of PORT timeline adherence	Care coordination
Patient Tracking	Real-time EMR tracking of care delivery processes	Informational support
Reporting	Monthly PORT delay run charts at Tumor Board	Informational support

BRP: Barrier reduction plan, EMR: electronic medical record, HNC: Head and neck cancer, PORT: Postoperative radiation therapy, SC: South Carolina

Culture, the set of shared and socially transmitted beliefs and values regarding the nature of time, social relationships, and supernatural entities that are passed between generations and shared among members of ethnic and racial groups[34] is a critical determinant of cancer prevention, control, and treatment behaviors as well as cancer-related psychological and behavioral outcomes[35]. As a result, NDURE navigation sessions and intervention components will be delivered in a culturally appropriate manner. We will also use validated measures of key cultural variables to understand the role that culture plays in the delivery, acceptability, and clinical impact of NDURE.

6.1.2 ADMINISTRATION AND/OR DOSING

NDURE will be delivered in one-on-one, face-to-face sessions between the navigator and the participant in a clinic- or hospital-based setting. The NDURE intervention consists of three in-person navigation sessions, which are expected to take 30-60 minutes each. The three clinic- or hospital-based sessions will coincide with the presurgical consult, hospital discharge, and 1st postoperative clinic visit, time points chosen to facilitate case identification and coordination across key care transitions. Contact beyond the three prescribed in-person sessions will occur with a frequency and modality (e.g. text message, email, etc.) dictated by patient and navigator need. A single dedicated navigator with no competing clinical or administrative responsibilities outside of this trial will deliver the NDURE intervention. Full-dose will consist of completing all three NDURE navigation sessions.

6.2 FIDELITY

6.2.1 INTERVENTIONIST TRAINING AND TRACKING

The navigator, supervised by Dr. Graboyes, will keep a tracking log with encounters (number, modality of each session), time (direct with patient, indirect to complete BRP), barriers (number, type), and BRP activity (action, outcome)[31]. In-person NDURE sessions will be audio-recorded and randomly selected sessions (20%) will be reviewed by Dr. Graboyes to ensure fidelity. Bi-monthly case conferences with the navigator, Dr. Graboyes, and Dr. Hughes-Halbert will further ensure continued high-quality PN.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

N/A

6.4 STUDY INTERVENTION/EXPERIMENTAL MANIPULATION ADHERENCE

Participants' adherence with study procedures will be tracked by attendance at intervention visits.

6.5 CONCOMITANT THERAPY

N/A

6.5.1 RESCUE THERAPY

N/A

7 STUDY INTERVENTION/EXPERIMENTAL MANIPULATION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL.

7.1 DISCONTINUATION OF STUDY INTERVENTION/EXPERIMENTAL MANIPULATION

N/A

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants are free to withdraw from participation in the study at any time upon request.
An investigator may discontinue a participant from the study for the following reasons:

- Significant study intervention non-compliance, unless varying compliance is an aspect of the study objectives

- Lost-to-follow up; unable to contact subject (see **Section 7.3, Lost to Follow-Up**)
- Any event or medical condition or situation occurs such that continued collection of follow-up study data would not be in the best interest of the participant or might require an additional treatment that would confound the interpretation of the study
- The participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation

The reason for participant discontinuation or withdrawal from the study will be recorded on the Case Report Form (CRF). Subjects who sign the informed consent form and are assigned to the study intervention but do not receive the study intervention may be replaced. Subjects who sign the informed consent form and receive the study intervention, and subsequently withdraw, or are discontinued from the study, will be replaced in the following circumstances as described in (**Section 5.4, Screen Failures**)

- Patient is expected to have surgery and then decides to pursue a nonsurgical treatment
- Patient is expected to have surgery at MUSC and then decides to pursue treatment elsewhere
- PORT is expected based on the clinical TNM classification, but analysis of the pathology specimen after surgery changes the pathologic TNM classification and/or adverse features such that PORT is not indicated per National Comprehensive Cancer Network (NCCN) Guidelines.

7.3 LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if he or she fails to return for two scheduled visits and study staff are unable to contact the participant after at least 3 attempts.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site will attempt to contact the participant, reschedule the missed visit within 2 weeks, counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts will be documented in the participant's medical record or study file.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 ENDPOINT AND OTHER NON-SAFETY ASSESSMENTS

Primary Endpoint

Initiation of postoperative PORT > 6 weeks after surgery is defined as more than 42 calendar days from the time of the definitive surgical resection to the initiation of radiation therapy. In situations in which the surgical management of the primary tumor and the neck are staged (i.e. occur on two different calendar days), the date of the surgery for the primary tumor will be used. In situations in which an additional surgical resection is required (e.g. re-resection of positive margins to clear residual disease), the date of the earlier (i.e. attempted definitive) surgical procedure will be used to determine the target start date for PORT.

Secondary Endpoints

Clinical Outcomes

Racial disparities in initiation of PORT > 6 weeks after surgery is defined as the difference in the rate of initiation of PORT > 6 weeks after surgery between white and AA HNC patients.

Days between surgery and the start of PORT is defined as the time, in days, between the date of definitive surgical resection to the initiation of radiation therapy. All of the criteria used to adjudicate the date of the definitive surgical procedure described for the primary outcome measure will be applied to this measure.

Barriers resolved is the number of barriers identified by the navigator that are resolved during the NDURE intervention, as determined by the navigator log.

Unresolved barriers is the number of barriers identified by the navigator that are not resolved during the NDURE intervention, as determined by the navigator log.

Pre-Surgical Radiation Consultation is defined as the attendance by the patient at a consultation with a radiation oncologist (at MUSC or elsewhere) prior to surgery to discuss RT in the definitive or adjuvant setting

Pre-Radiation Therapy Dental Extractions is defined as the extraction of teeth prior to discharge from the index hospitalization for the definitive surgical procedure. Patients who are edentulous are not evaluable for this measure.

Surgery to Pathology Report </= 7 days is defined as the production of the pathology report from the definitive surgical procedure within the EMR within 7 calendar days of the definitive surgical procedure. Addenda to the pathology report at the request of the HNC team (e.g. tumor p16 status) are not counted in this measure.

Surgery to PORT Referral </= 10 days is defined as the placement of a referral for PORT, at MUSC or elsewhere, within 10 calendar days of the definitive surgical procedure.

RT Referral to Consult </= 10 days is defined as the evaluation of the patient at a postoperative consultation with a radiation oncologist within 10 calendar days of the referral being placed (or postoperative appointment being scheduled in cases in which care has been established and the return visit is no longer a consultation). The consultation may occur in the clinic or the hospital depending upon clinical circumstances.

RT Consult to Initiation </= 21 days is defined as the initiation of PORT within 21 calendar days of the patient being evaluated by a radiation oncologist for PORT.

Feasibility

NDURE Accrual is defined as the proportion of eligible patients who enroll in NDURE

NDURE Completion is defined as a participant completing the baseline assessment, at least two NDURE intervention sessions, and the final follow-up assessment

Navigation Session Completion is the number of NDURE navigation sessions completed by a participant

Navigator Caseload is the number of simultaneous cases (on-trial participants) being navigated by the NDURE navigator

Navigator Time Allocation (Direct) is the time (in minutes), that the NDURE navigator spends directly interacting with the patient to identify and address barriers to timely, equitable postoperative radiation therapy

Navigator Time Allocation (Indirect) is the time (in minutes), that the navigator spends generating and enacting each Barrier Reduction Plan that is not directly interacting with the patient

Acceptability

Satisfaction with the Interpersonal Relationship with the Navigator Scale is, a validated, 9-item measure of the satisfaction of the interpersonal relationship with the patient navigator that has been used in prior studies of PN[36,37].

Satisfaction with Logistical Aspects of Navigation Scale is a validated, 26-item measure of the satisfaction of the logistical aspects of PN that has been used in prior studies of PN[38].

Health Behavior Constructs

Care Transition Measure-15 (CTM-15) is a validated, psychometrically sound 15-item, unidimensional measure of care transitions across the healthcare system that is consistent with the concept of patient-centeredness and useful from an organization perspective for the purpose of performance measurement and quality improvement[39]. Higher scores reflect higher levers of care integration and coordination.

Communication & Attitudinal Self-Efficacy Scale (CASE)-Cancer is a validated, psychometrically sound 12-item scale that addresses three domains of self-efficacy in cancer care (understanding and participating in care, maintaining a positive attitude, and seeking and obtaining information)[40]. The CASE-Cancer scale has been used extensively in PN studies to measure perceived self-efficacy[10,31,41]. Responses are on a 4-point Likert scale with higher scores indicating higher levels of self-efficacy.

Interpersonal Support Evaluation List-12 (ISEL-12) is a validated, 12-item assessment of three domains of interpersonal support[42] that has been used to assess support in prior PN studies[43]. Items are rated on a 4-point Likert scale with higher scores indicating more support.

Perceived Susceptibility Questionnaire is modified version of a validated 3-item perceived susceptibility subscale for mammography screening[44] to assess perceived susceptibility for delays starting PORT after HNC surgery. Items are rated on a 5-point Likert scale with higher scores indicating higher perceived susceptibility.

Illness Perception Questionnaire-Revised (IPQ-R) consequences subscale (HNC modification). The IPQ-R consequences subscale is easily modifiable to asses disease-specific perceived severity[45].The IPQ-R is a validated assessment of a patient's self-representation of the health consequences of their illness[46]. It is scored using a 5-point Likert scale with higher scores indicate higher perceived severity.

Perceived Barriers Questionnaire is a self-report measure of the presence/absence of pre-specified barriers to cancer care (yes/no). The questionnaire has been used extensively to assess perceived barriers in prior PN studies[11,31,41,47].

Covariates

Behavioral Risk Factor Surveillance Survey (BRFSS) Demographics. The BRFSS is the nation's premier health-related survey that collects data about health-related risk behaviors from US residents. The demographic section from the BRFSS will be used (in-person) to ascertain participant sex, age, race, marital status, insurance, educational attainment, living situation, zipcode, phones for personal use, employment, and annual household income[48].

BRFSS Tobacco Use and Alcohol Consumption. The tobacco use and alcohol consumption sections of the BRFSS will be used (in-person) to characterize total cigarette exposure, current cigarette use, quit attempts, days of alcohol consumption, average drinks/day, frequency of $\geq$ 5 drinks, and maximum number of drinks.

Clinical and Oncologic Characteristics. Clinical characteristics will include comorbid medical conditions, and cancer history. Oncologic characteristics will include HNC tumor subsite, HNC tumor histology, p16/human papillomavirus (HPV) tumor status, American Joint Committee on Cancer TNM Class and overall stage grouping, type of ablative surgery, type of reconstruction, treatment dates, facility of planned adjuvant therapy, and adjuvant treatment type planned (adjuvant radiation or chemoradiation).

Barrier Load Survey will measure 1) the number of barriers identified in the BRP during NDURE; and 2) the type of barrier in our modified version of existing PN logs[11,31,47]

Cultural Factor Survey is a validated, psychometrically sound questionnaire consists of three subscales assessing temporal orientation (5 items), collectivism (6 items), and religiosity (9 items)[49]. Prior PN studies have used these scales to measure cultural factors[50].

MD Anderson Symptom Inventory-Head Neck (MDASI-HN) is a validated, psychometrically sound, 28-item multi-symptom patient-reported outcome measure for clinical and research use that assesses the severity of symptoms experienced by patients with cancer (including 9 HNC-specific symptoms), and the associated interference with daily living caused by these symptoms. Higher scores indicate more severe symptom/symptom interference[51].

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

- Primary Endpoint(s):

Because this is a pilot study generating preliminary data, our single-arm trial is not powered to detect a pre-specified improvement (i.e. reduction) in the rate of delayed PORT with NDURE. As such, the primary endpoint will be assessed via descriptive statistics. Hypotheses will be generated from the preliminary data for testing in future studies.

- Secondary Endpoint(s):

Initiation of postoperative PORT > 6 weeks after surgery

We hypothesize that, compared to historical control data for patients undergoing surgery for HNC at MUSC followed by PORT between 2014-2016, patients who receive NDURE will have a decreased rate of PORT delays (initiation of PORT > 6 weeks after surgery).

Alternatively, our null hypothesis is that there will be no difference in the rate of PORT delay between patients who receive NDURE when compared to historical control data for patients undergoing surgery for HNC at MUSC followed by PORT between 2014-2016.

Initiation of postoperative PORT > 6 weeks after surgery

We hypothesize that, compared to historical control data for patients undergoing surgery for HNC followed by PORT in the National Cancer Database between 2006-2014, patients who receive NDURE will have a decreased rate of PORT delays (initiation of PORT > 6 weeks after surgery).

Alternatively, our null hypothesis is that there will be no difference in the rate of PORT delay between patients who receive NDURE when compared to historical control data for patients undergoing surgery for HNC followed by PORT in the National Cancer Database between 2006-2014.

9.2 SAMPLE SIZE DETERMINATION

Because this is a pilot study generating preliminary data, our single-arm trial is not powered to detect a pre-specified improvement (i.e. reduction) in the rate of delayed PORT with NDURE. Rather, we

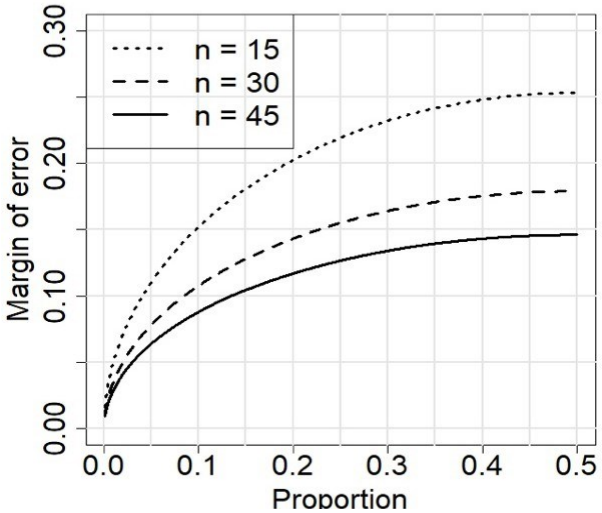


Figure 1. Margin of Error Rates of Delayed PORT. Margin of error for rates of delayed PORT for overall cohort and white and African American subgroups in the single-arm NDURE pilot study.

justify our sample size based on the desired precision (as measured by the half-width of a 95% CI, also known as the margin of error) in estimates of PORT delay rates. **Fig. 1** shows the margin of error for proportions ranging from 0 to 0.5 for n=15, 30 and 45 the sample sizes for AA and white patient subgroups and the entire cohort, respectively. Because the margin of error for proportion *p* is equivalent to that for proportion 1 – *p*, we limit Figure 1 to proportions ranging from 0 to 0.5.) For PORT delay rate estimates based on the entire sample, the maximum margin of error (smallest precision) is 0.15 occurring for a proportion of 0.5, with the margin of error decreasing (precision increasing) for proportions closer to 0 or 1. For example, the 95% CI for an observed PORT delay rate of 50% is 35% to 65%, indicating an acceptable level of uncertainty in the estimate and providing adequate precision to allow accurate design of a randomized trial evaluating the NDURE intervention. The margin of error is greatest for the subpopulation of AA patients because of the smaller sample size. Nonetheless, the maximum margin of error at an observed proportion of 50% is approximately 0.25 (95% CI = 25% to 75%) which is sufficient information to adequately design a randomized study to evaluate the efficacy of NDURE in these subpopulations. We considered extending the study accrual to increase enrollment to targets of 75 patients (white, n=50 and AA, n=25). The maximum margin of error for a proportion of 0.5 would decrease to 0.11 (relative to 0.15 with enrollment targets of n=45), which is a negligible improvement. The 95% CI for an observed PORT delay rate of 50% in the larger (n=75) cohort would be 39% to 61% (relative to 35% to 65% in the n=45 cohort), which again does not significantly improve precision in terms of accurate design of a randomized trial evaluating the NDURE intervention. The AA sub-population has the greatest margin of error because of the smaller sample size. By increasing enrollment from n=15 AAs to n=25 AAs, the margin of error would only decrease from 0.25 (95% CI = 25% to 75%) to 0.20 (95% CI = 30% to 70%) at an observed proportion of 50%, which again does not significantly improve the ability to design a randomized study to evaluate the efficacy of NDURE in these subpopulations. Given the volume of eligible patients at MUSC[33] and historical participation rates[52], we consider n=45 (AA n=15; white n=30) subjects to be a reasonable sample size target for patients who enroll and complete the study. This approach and data analysis plan recognizes that early phase trials do not produce definitive clinical conclusions[32], but provide information to ascertain whether additional large-scale clinical trials assessing efficacy are warranted and estimates of precision to inform future study design[53].

Every effort will be made to minimize missing data and lost-to-follow-up participants. Participants will complete assessments at baseline and post intervention using an iPad-based REDCap collection method. The program coordinator will attempt to contact patients at least three times using a variety of methods of communication (e.g. text message, phone call, email, mail, etc) to complete outcome measures. This method resulted in 100% instrument completion in prior studies conducted by our team. Patients in the ITT population for whom the primary endpoint is not evaluable due to loss to follow-up will be considered NDURE failures, and their time to PORT will be treated as exceeding 6 weeks for the purposes of analysis (a very conservative approach for this single-arm, phase II pilot study. In the event that missing data occur for other endpoints, we will address them via standard multiple imputation procedures. In general, less than 10% missing data has little impact on study power and does not induce bias regardless of the missing data mechanism. If missing data is greater than 10%, it will be imputed using Markov Chain Monte Carlo (MCMC) methods. The data augmentation will be applied to Bayesian inference with missing data by repeating imputation step (i.e., simulating the missing values based on the observation) and step for exploring the posterior distribution based on the complete sample estimates obtained from the imputation step.

Our plan to accrue 45 patients (white, n=30 and AA, n=15) to the study over 13 months is highly feasible. Based on data from MUSC/HCC for 2018, it is expected that 125 patients/year will be eligible for the study, of whom 28 (22%) are expected to be AA and 97 (78%) are expected to be white. Based on the PI and study team's prior experience recruiting and enrolling for similar studies embedded into clinical care, we anticipate that 50% of eligible patients will accrue to this study. Based on this 50% accrual rate, over the course of 13 months, we would expect to accrue 68 patients (n=15 AAs; n=53 white). Thus, by conservative estimates with appropriate over-sampling of AAs, our overall accrual target (n=45) and for the AA racial subgroup (n=15) appear highly feasible in the allocated 13 month accrual period.

9.3 POPULATIONS FOR ANALYSES

Prior to studying the NDURE intervention in a phase II clinical trial, we will pre-test our intervention in n=3 patients to ensure proper implementation into clinical workflow. These patients will participate in the intervention and outcome assessment only for the purposes of pre-testing and assessing our implementation into clinical workflow but not for the purposes of analysis towards any of the study endpoints.

For the efficacy analysis, we will utilize a modified intention-to-treat (ITT) population. Participants will be part of the modified ITT population as defined by the following criteria:

1. Randomized to NDURE or Usual Care
2. Receipt of curative intent surgery at MUSC
3. Indication for PORT (with or without concurrent chemotherapy) per NCCN Guidelines based on the presence of at least one of the following adverse features on final pathologic evaluation: ENE, positive margin, pT3 or pT4 primary, N2 or N3 nodal disease, nodal disease in levels IV or V, PNI or LVI

As such, the modified ITT analytic population addresses the fact that eligibility, registration, randomization, and delivery of a portion of the intervention (NDURE or Usual Care) occur prior to definitive treatment of the HNSCC. However, the primary study objective (and endpoint) are defined and evaluable only for patients who undergo surgery for HNSCC and have an indication for adjuvant therapy (which can only be definitively known following surgical resection). As such, we expect that a predictable subset of patients will be enrolled in the study, based on meeting all inclusion, be randomized to NDURE or Usual Care, receive a portion of the intervention (NDURE Visit 1) and then subsequently develop a study exclusion criterion based on interval information that becomes available later in the clinical course that cannot be known at the time of study enrollment and registration, namely:

- failure to undergo curative intent surgery at MUSC (exclusion criteria #4)
- lack of indication for PORT (with or without chemotherapy) per NCCN Guidelines (exclusion criteria #5)

As such, patients who meet study inclusion criteria but subsequently develop exclusion criteria #4 or #5 during the course of the study will be replaced since the primary endpoint is anchored to findings that occur after analysis of the pathologic specimen obtained during surgery. Patients in the modified ITT population for whom the primary endpoint is not evaluable due to loss to follow-up will be considered navigation failures, and their time to PORT will be treated as exceeding 6 weeks for the purposes of analysis.

We will also perform an efficacy analysis on the per-protocol analytic dataset, a subset of the modified ITT population who completed all 3 NDURE study sessions. These patients are judged to have complied with the protocol sufficiently to ensure that these data would be likely to represent the effects of the NDURE intervention according to the underlying scientific model.

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

We will construct graphical displays and calculate descriptive statistics (e.g. frequencies and percent for categorical variables, and mean, median, standard deviation, and range for continuous variables). Covariates will be specified below. For inferential tests, we will use a p-value of 0.05, two-sided, and 95% confidence intervals (CIs) to assess statistical significance (Type I error). Normality of the data will be assessed before underlying statistical procedures will be performed. We will evaluate variable transformations as needed to satisfy assumptions and consider transformations of variables to induce approximate normality and stabilize variance as needed. Nonparametric tests will be applied when appropriate.

9.4.2 ANALYSIS OF THE PRIMARY ENDPOINT(S)

For the primary endpoint, delays starting PORT, the proportion of patients who start PORT more than 6 weeks after surgery and corresponding 95% CI will be calculated for the overall cohort and for white and AA subgroups separately. We will calculate racial disparities in PORT delay by comparing the difference in the rate of PORT delay (more than 6 weeks after surgery) between white and AA patients.

9.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

We will analyze time-to-PORT as a continuous variable and estimate median time-to-PORT for the cohort overall and for AA and white subgroups using Kaplan-Meier curves with Greenwood variance estimation for the corresponding 95% CIs. We will calculate racial disparities in time-to-PORT by comparing the difference in median time-to-PORT between white and AA patients.

We will compare the findings from our phase II trial of NDURE (rate of PORT delay; median time-to-PORT for the cohort overall and for racial disparities in each endpoint) to historical controls (at MUSC[33] and nationally[6]) using Fisher's exact test. If the upper bound of the 95% CI for the rate of delayed PORT (and racial disparities in delayed PORT) is at or below the lower bound of the 95% CI for the similar endpoint in our historical controls, we can conclude that the preliminary estimates of the therapeutic activity of NDURE (i.e. clinical benefit) suggest that further rigorous testing of the efficacy of the PN intervention in a larger clinical trial is warranted based on these phase II results. We will nevertheless interpret findings relative to historical control cautiously given that the data do not arise from a randomized trial.

For the secondary endpoints of barrier reduction and unresolved barriers, we will calculate the proportion of unresolved barriers and the frequency of unresolved barriers (respectively) at the end of NDURE, consistent with prior PN studies[47]. We will use logistic regression to assess the relationship between unresolved barriers and the rate of PORT delay (primary endpoint), controlling for covariates listed in **Section 8.1.**

Secondary endpoints for feasibility, acceptability, fidelity and HNC care delivery will be analyzed as follows. For study accrual, we will calculate the proportion and frequency of eligible patients who accrue (overall, white, and AA). Given its pilot nature, the study is not designed to evaluate racial differences in accrual, although reasons for study decline will be collected, analyzed by race, and used to refine recruitment. NDURE completion will be analyzed as 1) the percentage of enrolled patients who attend all three in-person NDURE sessions and 2) the proportion of three in-person NDURE sessions that are completed. For navigator caseload, we will consider the frequency of simultaneous cases navigated. Navigator time allocation for direct and indirect time, as well as patient-report measures of satisfaction with navigation (acceptability) will be summarized as described above for continuous data. NDURE fidelity will be analyzed as the proportion of enrolled patients who have a BRP documented in the EMR. For HNC care delivery processes, we will calculate the proportion of patients receiving each key HNC care delivery process.

For secondary endpoints evaluating the theoretical constructs underlying NDURE (care coordination, support, perceived susceptibility, severity, barriers, and self-efficacy), we will estimate the mean change in each measure (pre-post) as well as standard deviations and 95% CIs for each; comparisons will be conducted using Wilcoxon sign-rank test. Baseline levels of each dependent variable will be controlled in each model; additional covariates will be considered by examining associations between potential covariates and each dependent variable using linear regression ($p < .10$ where the change in each outcome measure is the dependent variable). This method will allow estimation of intervention effects while adjusting for potential confounders.

9.4.4 SAFETY ANALYSES

N/A

9.4.5 BASELINE DESCRIPTIVE STATISTICS

N/A

9.4.6 PLANNED INTERIM ANALYSES

N/A

9.4.7 SUB-GROUP ANALYSES

Planned sub-group analyses of the primary endpoint will occur based on age and sex to evaluate the impact of inclusion across the lifespan and sex as a biologic variable. Historical data have not established an association between either age or sex with the primary endpoint[6]. Given the importance of race to the study objectives, analysis of the primary endpoint by race is evaluated as a secondary objective instead of planned subset analysis. Additional planned subset analyses will evaluate the impact of the NDURE intervention on the primary endpoint based on insurance status and fragmentation of care between the surgical facility and radiation facility, both of which have been described as risk factors for delayed PORT[6]. As such, both of these variables have the potential to confound the effect of the intervention were they to be imbalanced in a future RCT. As such, evaluating their impact on the primary endpoint in this study would allow for rational stratification in planned future RCTs.

9.4.8 TABULATION OF INDIVIDUAL PARTICIPANT DATA

Individual participant data will not be listed by measure and time point.

9.4.9 EXPLORATORY ANALYSES

N/A

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

We will obtain full written Informed consent from patients enrolling in the study. Informed consent will occur via face-face discussion between one of the study team members designated to perform informed consent and the potential study participant. After describing the study and allowing the potential participants to ask any questions, we will schedule interviews with those who are eligible and interested in participating in the study. Participant will have time to read the informed consent form and HIPAA document on their own. Consents will be written in simple, easy-to-understand language and obtained on the day of enrollment by the trained study coordinator. A study team member will answer any questions about the study and participants will be asked to sign the consent and HIPAA forms. All participants will sign informed consent forms before the interview. All participants will receive a copy of their informed consent and HIPAA forms for their records. The informed consent process will take place in a private room in the 10th floor Rutledge Tower Head and Neck Cancer Clinic or in a private room in the HCC. Only the study participant will provide informed consent. Subjects will be allowed up to one week to decide whether to participate in the study.

10.1.2 STUDY DISCONTINUATION AND CLOSURE

[This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants, investigator, funding agency, and regulatory authorities. If the study is prematurely terminated or suspended, the PI will promptly inform study participants, the IRB, and sponsor/funding agency and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Insufficient compliance of study staff to the protocol (e.g. significant protocol violations)
- Data that are not sufficiently complete and/or evaluable

The study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the funding agency, sponsor, IRB, Food and Drug Administration (FDA), or other relevant regulatory or oversight bodies (OHRP, data safety monitoring board (DSMB)).

10.1.3 CONFIDENTIALITY AND PRIVACY

To help protect participant confidentiality, we will assign a unique study ID number to each subject's information in place of his/her name and will label data collection forms only with the ID number. All hard copy and electronic files will be stored appropriately using double-locked methods and password-protection. Only the study team member will have access to study records. Participant data will be collected and recorded on either a password-protected electronic data capture format (Research Electronic Data Capture; REDCap) or paper-based forms depending upon patient preference. For the paper collection data method, the data collection form will be labeled only with the participant's unique study ID number, and then stored within locked drawers in a locked office. The information on these paper forms will be transferred to a password-protected REDCap database such that all data will be stored in the password-protected REDCap Database. Only members of the study team will have access to the data. We have no plan to use laptops, jump drives, CDs/DVDs to transport data.

10.1.4 FUTURE USE OF STORED SPECIMENS AND DATA

1. Data collected for this study will be analyzed and stored. After the study is completed, the de-identified, archived data will be transmitted to and stored.

10.1.5 KEY ROLES AND STUDY GOVERNANCE

Principal Investigator
Evan Graboyes, MD
Medical University of South Carolina
135 Rutledge Ave, MSC 550 Charleston, SC 29425
843-792-0719
graboyes@musc.edu

10.1.6 SAFETY OVERSIGHT

The PI will be responsible for overseeing safety data. Aggregate reviews will occur by the PI for all AEs, UPs, protocol violations, audit results, early withdrawals, whether the study accrual pattern warrants continuation/action, and endpoint data. Aggregate reviews will occur monthly.

10.1.7 CLINICAL MONITORING

N/A

10.1.8 QUALITY ASSURANCE AND QUALITY CONTROL

Each clinical site will perform internal quality management of study conduct, data and biological specimen collection, documentation and completion.

Quality control (QC) procedures will be implemented as follows:

Informed consent --- Study staff will review both the documentation of the consenting process as well as a percentage of the completed consent documents. This review will evaluate compliance with GCP, accuracy, and completeness. Feedback will be provided to the study team to ensure proper consenting procedures are followed.

Source documents and the electronic data --- Data will be initially captured on source documents (see **Section 10.1.9, Data Handling and Record Keeping**) and will ultimately be entered into the study database. To ensure accuracy site staff will compare a representative sample of source data against the database, targeting key data points in that review.

Intervention Fidelity — Consistent delivery of the study interventions will be monitored throughout the intervention phase of the study. Procedures for ensuring fidelity of intervention delivery are described in **Section 6.2.1, Interventionist Training and Tracking**.

Should independent monitoring become necessary, the PI will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor/funding agency, and inspection by local and regulatory authorities.

10.1.9 DATA HANDLING AND RECORD KEEPING

10.1.9.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection will be the responsibility of the clinical trial staff at the site under the supervision of the site investigator. The investigator will be responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All source documents will be completed in a neat, legible manner to ensure accurate interpretation of data. Hardcopies of the study visit worksheets will be provided for use as source document worksheets for recording data for each participant consented/enrolled in the study. Data recorded in the electronic case report form (eCRF) derived from source documents will be consistent with the data recorded on the source documents.

Clinical data (including AEs will be entered into REDCap. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

10.1.9.2 STUDY RECORDS RETENTION

In accordance with Health and Human Services regulation at 45 CFR 46.115(b), we will retain IRB records for at least three years. At the end of three years, records will be boxed, labeled, and sent to central storage for another three years. Research records will be retained for six years to allow evaluation and repetition by others of the results and to investigate an allegation of research misconduct.

10.1.10 PUBLICATION AND DATA SHARING POLICY

This study will be conducted in accordance with the following publication and data sharing policies and regulations:

NIH Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

This study will comply with the NIH Data Sharing Policy and Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration and Results Information Submission rule. As such, this trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals. Data from this study may be requested from other researchers x years after the completion of the primary endpoint by contacting <specify person or awardee institution, or name of data repository. Considerations for ensuring confidentiality of these shared data are described in **Section 10.1.3.**

10.2 ADDITIONAL CONSIDERATIONS

N/A

10.3 ABBREVIATIONS AND SPECIAL TERMS

AA	African American
AE	Adverse Event
AJCC	American Joint Committee on Cancer
BRFSS	Behavioral Risk Factor Surveillance Survey
BRP	Barrier Reduction Plan
CASE	Communication & Attitudinal Self-Efficacy
CFR	Code of Federal Regulations
CI	Confidence Interval
CRF	Case Report Form
CTM-15	Care Transition Method-15
DCC	Data Coordinating Center
DSMB	Data Safety Monitoring Board
eCRF	Electronic Case Report Forms
EMR	Electronic Medical Record
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HBM	Health Belief Model
HCC	Hollings Cancer Center
HIPAA	Health Insurance Portability and Accountability Act
HNC	Head and Neck Cancer
ICH	International Council on Harmonisation
IDE	Investigational Device Exemption
IND	Investigational New Drug Application
IPQ-R	Illness Perception Questionnaire-Revised
IRB	Institutional Review Board
ISEL-12	Interpersonal Support Evaluation List-12
ITT	Intention-To-Treat
MDASI-HN	MD Anderson Symptom Inventory-Head Neck
MOP	Manual of Procedures
MUSC	Medical University of South Carolina
NCI	National Cancer Institute
NCCN	National Comprehensive Cancer Network
NCT	National Clinical Trial
NDURE	Navigation for Disparities and Untimely Radiation thErapy
NIH	National Institutes of Health
OHRP	Office for Human Research Protections
PI	Principal Investigator
PN	Patient Navigation
PORT	Postoperative Radiation Therapy
QA	Quality Assurance
QC	Quality Control
RCT	Randomized Controlled Trial
REDCap	Research Electronic Data Capture
RT	Radiation Therapy
SAE	Serious Adverse Event

SOA	Schedule of Activities
UP	Unanticipated Problem
US	United States

10.4 PROTOCOL AMENDMENT HISTORY

Document	Date of Issue	Summary of Change
Protocol Version 3.0	31-Jul-2019	Refined inclusion and exclusion criteria to reflect changes to 8th edition AJCC Staging for HPV-related oropharynx carcinoma as well screen failure definition; revised screen failure definition and efficacy analysis population from ITT to modified ITT
Protocol Version 2.0	17-Jun-2019	Protocol reformatted using the NCI Behavioral Protocol Template. In doing so, we refined the study objectives, definitions of endpoints, and analytic population.
Original Protocol	20-Sept-2019	

11 REFERENCES

1. Society AC. Cancer Facts & Figures 2018. Available at: *https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2018/cancer-facts-and-figures-2018.pdf*. Accessed February 26 2018.

2. Molina MA, Cheung MC, Perez EAet al. African American and poor patients have a dramatically worse prognosis for head and neck cancer: an examination of 20,915 patients. Cancer 2008; 113:2797-2806.

3. Guttmann DM, Kobie J, Grover Set al. National disparities in treatment package time for resected locally advanced head and neck cancer and impact on overall survival. Head Neck 2018; 40:1147-1155.

4. Ho AS, Kim S, Tighiouart Met al. Quantitative survival impact of composite treatment delays in head and neck cancer. Cancer 2018; 124:3154-3162.

5. Network NCC. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines): Head and Neck Cancers. Fort Washington, PA: National Comprehensive Cancer Network, 2017.

6. Graboyes EM, Garrett-Mayer E, Sharma AK, Lentsch EJ, Day TA. Adherence to National Comprehensive Cancer Network guidelines for time to initiation of postoperative radiation therapy for patients with head and neck cancer. Cancer 2017; 123:2651-2660.

7. Graboyes EM, Garrett-Mayer E, Ellis MAet al. Effect of time to initiation of postoperative radiation therapy on survival in surgically managed head and neck cancer. Cancer 2017; 123:4841-4850.

8. Graboyes E, Kompelli A, Neskey Det al. Association of Treatment Delays with Survival for Patients with Head and Neck Cancer. JAMA otolaryngology-- head & neck surgery 2019; 145:166-177.

9. Teng MS, Gupta V. Timely Adjuvant Postoperative Radiotherapy: Racing to a PORT in the Storm. JAMA otolaryngology--head & neck surgery 2018.

10. Freund KM, Battaglia TA, Calhoun Eet al. Impact of patient navigation on timely cancer care: the Patient Navigation Research Program. J Natl Cancer Inst 2014; 106:dju115.

11. Paskett ED, Katz ML, Post DMet al. The Ohio Patient Navigation Research Program: does the American Cancer Society patient navigation model improve time to resolution in patients with abnormal screening tests? Cancer Epidemiol Biomarkers Prev 2012; 21:1620-1628.

12. Guadagnolo BA, Dohan D, Raich P. Metrics for evaluating patient navigation during cancer diagnosis and treatment: crafting a policy-relevant research agenda for patient navigation in cancer care. Cancer 2011; 117:3565-3574.

13. Siegel RL, Miller KD, Jemal A. Cancer Statistics, 2017. CA Cancer J Clin 2017; 67:7-30.

14. Murphy CT, Galloway TJ, Handorf EAet al. Survival Impact of Increasing Time to Treatment Initiation for Patients With Head and Neck Cancer in the United States. J Clin Oncol 2016; 34:169-178.

15. Cramer JD, Speedy SE, Ferris RL, Rademaker AW, Patel UA, Samant S. National evaluation of multidisciplinary quality metrics for head and neck cancer. Cancer 2017; 123:4372-4381.

16. Ang KK, Trotti A, Brown BWet al. Randomized trial addressing risk features and time factors of surgery plus radiotherapy in advanced head-and-neck cancer. Int J Radiat Oncol Biol Phys 2001; 51:571-578.

17. Huang J, Barbera L, Brouwers M, Browman G, Mackillop WJ. Does delay in starting treatment affect the outcomes of radiotherapy? A systematic review. J Clin Oncol 2003; 21:555-563.

18. Bernier J, Domenge C, Ozsahin Met al. Postoperative irradiation with or without concomitant chemotherapy for locally advanced head and neck cancer. N Engl J Med 2004; 350:1945-1952.

19. Cooper JS, Pajak TF, Forastiere AAet al. Postoperative concurrent radiotherapy and chemotherapy for high-risk squamous-cell carcinoma of the head and neck. N Engl J Med 2004; 350:1937-1944.

20. Shew M, New J, Bur AM. Machine Learning to Predict Delays in Adjuvant Radiation following Surgery for Head and Neck Cancer. Otolaryngol Head Neck Surg 2019:194599818823200.

21. Chen MM, Harris JP, Orosco RK, Sirjani D, Hara W, Divi V. Association of Time between Surgery and Adjuvant Therapy with Survival in Oral Cavity Cancer. Otolaryngol Head Neck Surg 2018; 158:1051-1056.

22. Amini A, Stokes WA, Jones BLet al. Postoperative radiation performed at the same surgical facility associated with improved overall survival in oral cavity squamous cell carcinoma. Head Neck 2019.

23. Houlton JJ. Defining Optimal Treatment Times in Head and Neck Cancer Care: What Are We Waiting For? JAMA otolaryngology-- head & neck surgery 2018.

24. Divi V, Chen MM, Hara Wet al. Reducing the Time from Surgery to Adjuvant Radiation Therapy: An Institutional Quality Improvement Project. Otolaryngol Head Neck Surg 2018; 159:158-165.

25. Battaglia TA, Bak SM, Heeren Tet al. Boston Patient Navigation Research Program: the impact of navigation on time to diagnostic resolution after abnormal cancer screening. Cancer Epidemiol Biomarkers Prev 2012; 21:1645-1654.

26. Robinson-White S, Conroy B, Slavish KH, Rosenzweig M. Patient navigation in breast cancer: a systematic review. Cancer Nurs 2010; 33:127-140.

27. Natale-Pereira A, Enard KR, Nevarez L, Jones LA. The role of patient navigators in eliminating health disparities. Cancer 2011; 117:3543-3552.

28. Brooke BS, Slager SL, Swords DS, Weir CR. Patient and caregiver perspectives on care coordination during transitions of surgical care. Transl Behav Med 2018; 8:429-438.

29. Rodday AM, Parsons SK, Snyder Fet al. Impact of patient navigation in eliminating economic disparities in cancer care. Cancer 2015; 121:4025-4034.

30. Taylor JM, Braun TM, Li Z. Comparing an experimental agent to a standard agent: relative merits of a one-arm or randomized two-arm Phase II design. Clin Trials 2006; 3:335-348.

31. Freund KM, Battaglia TA, Calhoun Eet al. National Cancer Institute Patient Navigation Research Program: methods, protocol, and measures. Cancer 2008; 113:3391-3399.

32. Green S, Benedetti J, Smith A, Crowley J. Clinical Trials in Oncology. Boca Raton, FL.: CRC Press, 2012.

33. Janz T, Kim J, Hill Eet al. Association of Care Processes with Timely, Equitable Postoperative Radiotherapy in Patients with Surgically Treated Head and Neck Squamous Cell Carcinoma. JAMA otolaryngology-- head & neck surgery 2018; 144:1-10.

34. Koltko-Rivera ME. The Psychology of Worldviews. Rev Gen Psychol 2004; 8:3-58.

35. Hughes C, Fasaye GA, LaSalle VH, Finch C. Sociocultural influences on participation in genetic risk assessment and testing among African American women. Patient Educ Couns 2003; 51:107-114.

36. Jean-Pierre P, Fiscella K, Freund KMet al. Structural and reliability analysis of a patient satisfaction with cancer-related care measure: a multisite patient navigation research program study. Cancer 2011; 117:854-861.

37. Jean-Pierre P, Fiscella K, Winters PCet al. Psychometric development and reliability analysis of a patient satisfaction with interpersonal relationship with navigator measure: a multi-site patient navigation research program study. Psychooncology 2012; 21:986-992.

38. Carle AC, Jean-Pierre P, Winters Pet al. Psychometric evaluation of the patient satisfaction with logistical aspects of navigation (PSN-L) scale using item response theory. Med Care 2014; 52:354-361.

39. Coleman EA, Mahoney E, Parry C. Assessing the quality of preparation for posthospital care from the patient's perspective: the care transitions measure. Med Care 2005; 43:246-255.

40. Wolf MS, Chang CH, Davis T, Makoul G. Development and validation of the Communication and Attitudinal Self-Efficacy scale for cancer (CASE-cancer). Patient Educ Couns 2005; 57:333-341.

41. Krok-Schoen JL, Brewer BM, Young GSet al. Participants' barriers to diagnostic resolution and factors associated with needing patient navigation. Cancer 2015; 121:2757-2764.

42. Cohen S, Mermelstein R, Kamarck T, Hoberman HM. Measuring the Functional Components of Social Support. In: I.G. S, B.R. S, eds. *Social Support: Theory, Research and Applications*. The Hague, Holland: Martinus Nijhoff, 1985:73-94.

43. Madore S, Kilbourn K, Valverde P, Borrayo E, Raich P. Feasibility of a psychosocial and patient navigation intervention to improve access to treatment among underserved breast cancer patients. Support Care Cancer 2014; 22:2085-2093.

44. Champion VL. Revised susceptibility, benefits, and barriers scale for mammography screening. Res Nurs Health 1999; 22:341-348.

45. Miles A. Perceived Severity. Available at: *https://cancercontrol.cancer.gov/brp/research/constructs/perceived_severity.html*. Accessed March 21 2019.

46. Moss-Morris R, Weinman J, Petrie KJ, Horne R, Cameron LD, Buick D. The Revised Illness Perception Questionnaire (IPQ-R). Psychol Health 2002; 17:1-16.

47. Ramachandran A, Snyder FR, Katz MLet al. Barriers to health care contribute to delays in follow-up among women with abnormal cancer screening: Data from the Patient Navigation Research Program. Cancer 2015; 121:4016-4024.

48. (CDC) CfDCaP. Behavioral Risk Factor Surveillance System Survey Questionnaire. Atlanta, GA.: U.S. Department of Health and Human Services, 2016.

49. Lukwago SN, Kreuter MW, Bucholtz DC, Holt CL, Clark EM. Development and validation of brief scales to measure collectivism, religiosity, racial pride, and time orientation in urban African American women. Fam Community Health 2001; 24:63-71.

50. Halbert CH, Briggs V, Bowman Met al. Acceptance of a community-based navigator program for cancer control among urban African Americans. Health Educ Res 2014; 29:97-108.

51. Rosenthal DI, Mendoza TR, Chambers MSet al. Measuring head and neck cancer symptom burden: the development and validation of the M. D. Anderson symptom inventory, head and neck module. Head Neck 2007; 29:923-931.

52. Graboyes EM, Kallogjeri D, Zerega Jet al. Association of a Perioperative Education Program With Unplanned Readmission Following Total Laryngectomy. JAMA otolaryngology-- head & neck surgery 2017.

53. Piantadosi S. Clinical Trials: A Methodologic Perspective. Hoboken, NJ: John Wiley & Sons, 2005.