A Single-Site, Parallel-Group, Randomized-Controlled Trial of Navigation Versus Usual Care for The Management of Delays and Racial Disparities Starting Postoperative Radiation Therapy in Adults with Surgically-Managed, Locally Advanced Head and Neck Squamous Cell Carcinoma (NDURE 2.0)

Protocol Number: 103161

National Clinical Trial (NCT) Identified Numbers: NCT04098458 (Single-Arm NDURE Feasibility Study) and NCT04030130 (RCT of NDURE vs UC)

Principal Investigator: Evan Graboyes, MD, MPH

Sponsor: Hollings Cancer Center

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

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Funded by: NCI

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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 Acceptance of this document constitutes agreement by the recipient that no unpublished information contained herein will be published or disclosed without prior approval of the Principal Investigator or other participating study leadership and as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 NIH terms of award.

PROTOCOL VERSION HISTORY

Section 1.3 Schedule of Activities (SOA): Added PORT delay nomogram to Study Visit 1

4.2.3 Justification for Intervention: Clarified the rationale for including telemedicine NDURE sessions in addition to face to face NDURE sessions as a response to the COVID-19 pandemic

6.1.1. Study Intervention Description: Added the possibility of conducting certain NDURE sessions via telemedicine instead of face to face as a response to the COVID-19 pandemic

Section 8.1 Endpoints and other non-Safety Assessments: Clarified that comorbidity will be assessed using the ACE-27. Added PORT delay nomogram as a covariate.

Section 10.4 Protocol Amendment History: Updated to reflect protocol revisions noted herein.

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STATEMENT OF COMPLIANCE

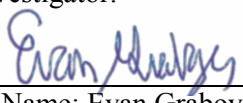
The trial will be conducted in accordance with International Council on Harmonisation Good Clinical Practice (ICH GCP), applicable United States (US) Code of Federal Regulations (CFR), and the National Cancer Institute (NCI) Terms and Conditions of Award. The Principal Investigator (PI) will assure that 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: 5/26/2020

Name: Evan Graboyes

Title: A Single-Site, Parallel-Group, Randomized-Controlled Trial of Navigation Versus Usual Care for The Management of Delays and Racial Disparities Starting Postoperative Radiation Therapy in Adults with Surgically-Managed, Locally Advanced Head and Neck Squamous Cell Carcinoma (NDURE 2.0)

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1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title: A Single-Site, Parallel-Group, Randomized-Controlled Trial of Navigation Versus Usual Care for The Management of Delays and Racial Disparities Starting Postoperative Radiation Therapy in Adults with Surgically-Managed, Locally Advanced Head and Neck Squamous Cell Carcinoma (NDURE 2.0)

Grant Number: K08CA237858-01A1

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), a multi-level, theory-based navigation intervention to improve timely, equitable post-operative radiation treatment (PORT) among patients with Head and Neck Squamous Cell Carcinoma (HNSCC). We hypothesize that NDURE will be feasible, acceptable, improve the timeliness of PORT for white and African American (AA) HNSCC patients and decrease disparities in delay between the two groups by improving system-, interpersonal-, and individual-level health behavior constructs.

Objectives:

Primary Objective (NDURE feasibility study):
1. To assess the feasibility of NDURE among white and AA HNSCC patients.

Secondary Objectives (NDURE feasibility study):
1. To assess the acceptability of NDURE to white and AA HNSCC patients and providers.
2. To determine the feasibility of a single dedicated navigator to manage a caseload of patients for the NDURE intervention
3. To evaluate the feasibility of collecting pre- and post-NDURE intervention outcome measures in this patient population

Primary Objective (RCT of NDURE vs Usual Care):
1. To evaluate the preliminary clinical impact of NDURE compared with usual care (UC) on delays starting PORT among white and AA HNSCC patients.

Secondary Objectives (RCT of NDURE vs Usual Care):
1. To evaluate the preliminary clinical impact of NDURE compared with UC on racial disparities in delays starting PORT among white and AA HNSCC patients.
2. To assess the preliminary clinical impact of NDURE compared with UC on barriers to care
3. To determine the preliminary impact of NDURE compared with UC on cancer care delivery processes.
4. To evaluate the preliminary behavioral mechanism of action of NDURE.

Endpoints:

Primary Endpoint:
PORT Delay

Secondary Endpoints:
NDURE Accrual Rate
NDURE Completion Rate
Navigation Session Completion Rate
Questionnaire Completion Rate

Navigator Caseload
Navigator Time Allocation (Direct)
Navigator Time Allocation (Indirect)

Patient Satisfaction with the Interpersonal Relationship with the Navigator Scale Score
Patient Satisfaction with Logistical Aspects of Navigation Scale Score

Time-to-PORT Initiation

Rate of Barrier Resolution
Unresolved Barriers Rate

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

Care Transition Measure-15 Score
Change from Baseline in Interpersonal Support Evaluation List-12 Score
Change from Baseline in Perceived Susceptibility Questionnaire Scores
Change from Baseline in Illness Perception Questionnaire-Revised Consequences Sub-Scale Score
Change from Baseline in Perceived Barriers Scale
Change from Baseline in Communication & Attitudinal Self-Efficacy Scale-Cancer Score

Study Population: The study population will consist of patients 18 years of age or older, male and female sex, and self-identified white and AA race, with locally advanced HNSCC undergoing curative intent surgery followed by PORT with or without concurrent chemotherapy

Phase or Stage: N/A

Description of Sites/Facilities Enrolling Participants:	The study will be conducted, and participants enrolled, at the Medical University of South Carolina (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 HNSCC clinical care.
Description of Study Intervention/Experimental Manipulation:	NDURE is a theory-based, multi-level patient navigation (PN) intervention consisting of three sessions of manualized PN with multiple intervention components that target system-(care coordination), interpersonal-(social support), and individual- (health belief model); perceived susceptibility, severity, barriers, self-efficacy) level health behavior theoretical constructs to reduce barriers to care, enhance HNSCC care delivery, and improve clinical outcomes (timely, equitable PORT). NDURE will be delivered from surgical consultation to PORT initiation (~3 months). The three 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:	NDURE Feasibility: 7 months NDURE vs Usual Care RCT: 42 months
Participant Duration:	3 months

1.2 SCHEMA

1.2.1 NDURE FEASIBILITY STUDY

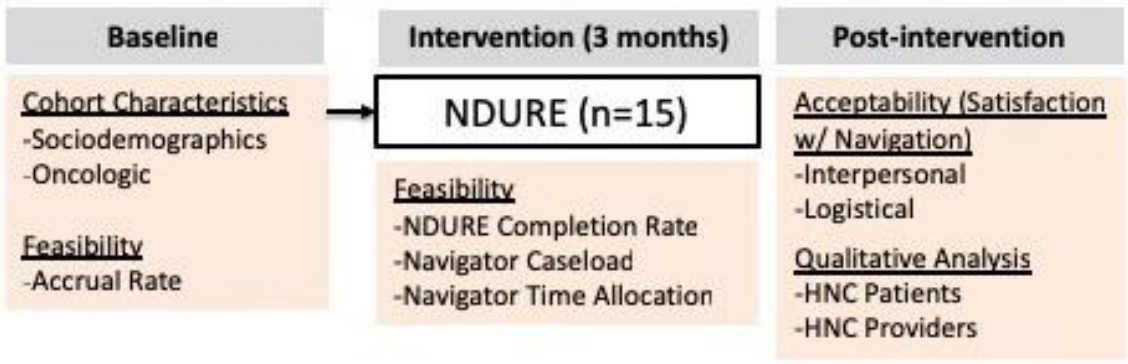

Figure 1. Feasibility Study Schema. Following completion of baseline questionnaires, participants (n=15) will be enrolled into NDURE. Measures of feasibility (enrollment, dropout, missed patient navigation (PN) encounters, navigator caseload and time allocation) will be assessed during the intervention delivery. Following completion of NDURE, patients will complete validated measures of acceptability related to Satisfaction with PN, and patients and providers will undergo semi-structured interview to help refine NDURE.

1.2.2 RCT OF NDURE VERSUS USUAL CARE

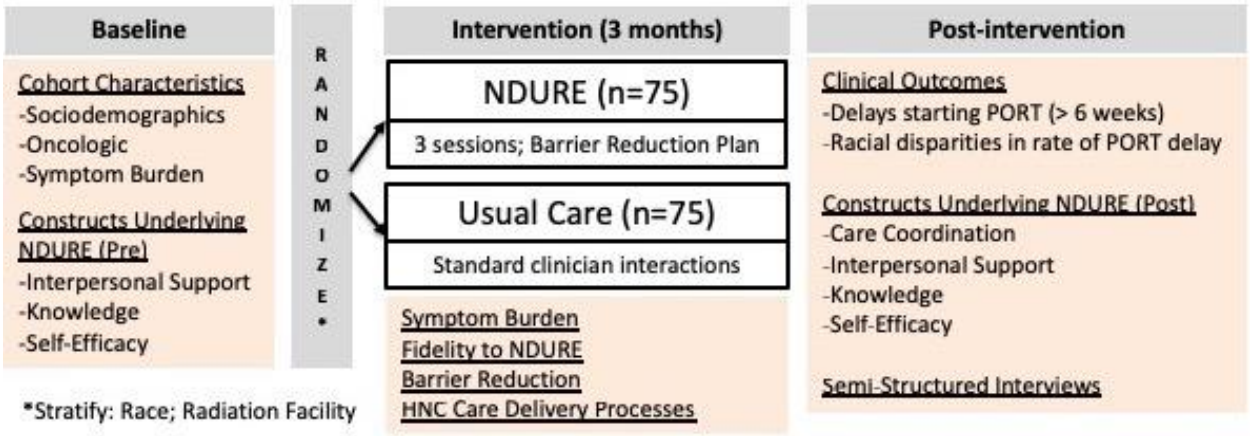

Figure 2. RCT Schema. HNSCC patients undergoing surgery and PORT will be enrolled into a pilot RCT comparing NDURE to usual care to evaluate the preliminary clinical impact of NDURE on delays and racial disparities starting PORT after HNSCC surgery.

1.3 SCHEDULE OF ACTIVITIES

Table 1. Schedule of Activities for NDURE and Usual Care and Follow-up

	Pre-screening	Visit 1	Visit 2 (Pre-Op)	Visit 3 (Pre-Discharge)	Visit 4 (Post-Discharge)	Visit 5 (Start of PORT)
Informed Consent						
Electronic Medical Record (EMR) Review Eligibility	X					
Informed Consent		X				
Study Procedures						
Randomization		X				
Demographics		X				
Clinical and Oncologic History		X			X	X
PORT Delay Nomogram		X				
Cultural Factor Survey		X				
Monitoring						
AE/SAE Assessment			X	X	X	X
Intervention Administration						
NDURE or UC			X	X	X	
Efficacy Evaluation						
PORT Delay						X
Feasibility						
NDURE Accrual	X					
NDURE Completion						X
Navigator Caseload		<---------->				
Navigator Time Allocation		<---------->				
Acceptability						
Satisfaction with the Interpersonal Relationship with the Navigator Scale						X
Satisfaction with Logistical Aspects of Navigation Scale						X
Program Evaluation						X
Cancer Care Delivery Processes						
Timely Care Processes		<---------->				
Health Behavior Constructs						
Barrier Reduction				X	X	X
Unresolved Barriers			X	X	X	X
Care Transition Measure-15				X	X	

Interpersonal Support Evaluation List-12		X				X
Perceived Susceptibility Questionnaire		X		X	X	
Illness Perception Questionnaire-Revise Consequences Subscale		X		X	X	
Perceived Barriers Questionnaire		X		X	X	X
Communication & Attitudinal Self-Efficacy Scale-Cancer		X				X
Navigator Barrier Log		X		X	X	X

2 INTRODUCTION

2.1 STUDY RATIONALE

Head and neck squamous cell carcinoma (HNSCC) 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]. HNSCC is also a disease with significant racial disparities in mortality; African Americans (AAs) have a 51% relative decrease in survival compared with whites[2]. Delays starting postoperative radiation therapy (PORT) after HNSCC surgery are a key driver of high mortality for all HNSCC 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 HNSCC patients[6], is 31% more common in AA HNSCC 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 HNSCC 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 (**N**avigation for **D**isparities and **U**ntimely **R**adiation th**E**rapy), our multi-level, theory-based PN intervention to improve timely, equitable PORT among HNSCC patients.

2.2 BACKGROUND

2.2.1 HEAD AND NECK SQUAMOUS CELL CARCINOMA

HNSCC, 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 HNSCC, 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 PORT and concurrent chemotherapy[5], outcomes remain poor with only 50% of patients with locally-advanced HNSCC surviving 5 years[1]. HNSCC is also a disease with significant racial disparities in mortality; AAs with HNSCC have a 19% absolute decrease in 5-year survival relative to white HNSCC patients[13] and a 51% relative decrease in survival[2].

2.2.2 DELAYS IN CANCER CARE DELIVERY FOR PATIENTS WITH HNSCC

Delays starting PORT contribute to high mortality in HNSCC and racial disparities in survival. Delays in cancer care delivery are a key driver of mortality for HNSCC patients[14] and a source of racial disparities in survival for AAs[3]. The critical time period for HNSCC patients is the time from surgery to the start of PORT[8,15], the only aspect of timely HNSCC care incorporated in National Comprehensive Cancer Network (NCCN) Guidelines (≤ 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 HNSCC trials[18,19]. Unfortunately, delays starting PORT affect 56% of HNSCC 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 HNSCC patients is a source of preventable mortality and contributes to racial disparities in survival[7].

2.2.3 BARRIERS TO TIMELY, EQUITABLE PORT AFTER SURGERY FOR HNSCC

The barriers that contribute to delays and racial disparities starting PORT after HNSCC 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 HNSCC patients has been impeded. To prevent continued treatment delays, it is critically important to identify the barriers to delivering timely, equitable PORT.

2.2.4 INTERVENTIONS TO IMPROVE TIMELY, EQUITABLE PORT FOR PATIENTS WITH HNSCC

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 HNSCC 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 HNSCC patients is crucial to improving survival for all HNSCC patients and decreasing racial disparities in mortality.

2.2.5 RATIONALE FOR PATIENT NAVIGATION TO IMPROVE TIMELY, EQUITABLE PORT

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 HNSCC surgery[8], we will develop and test NDURE, our multi-level, theory-based PN intervention to improve timely, equitable PORT among HNSCC patients. The underlying scientific premise is that our NDURE PN intervention has the potential to decrease delays starting PORT among HNSCC 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 HNSCC, 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 Hollings Cancer Center (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 HNSCC surgery and decrease racial disparities in timely HNSCC care. However, although we hypothesize a direct benefit to participants in the NDURE study (in terms of timely HNSCC 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 HNSCC 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

Table 1. Study Objectives and Endpoints

OBJECTIVES	ENDPOINTS
NDURE FEASIBILITY STUDY	
Primary	
To assess the feasibility of NDURE among white and AA HNSCC patients.	NDURE Accrual Rate
	NDURE Completion Rate
	NDURE Session Completion Rate
	Questionnaire Completion Rate
Secondary	
To assess the acceptability of NDURE to white and AA HNSCC patients and HNSCC providers.	Patient Satisfaction with the Interpersonal Relationship with the Navigator Scale Score
	Patient Satisfaction with Logistical Aspects of Navigation Scale Score
To determine the feasibility of a single dedicated navigator to manage a caseload of patients for the NDURE intervention	Navigator Caseload
	Navigator Time Allocation (Direct)
	Navigator Time Allocation (Indirect)
To evaluate the feasibility of collecting pre- and post-NDURE intervention outcome measures in this patient population	Study questionnaire completion rate
RCT of NDURE VERSUS USUAL CARE	
Primary	
To evaluate the preliminary clinical impact of NDURE compared with UC on delays starting PORT among white and AA HNSCC patients.	PORT Delay
	Time-to-PORT (TTP) Initiation
Secondary	
To evaluate the preliminary clinical impact of NDURE compared with UC on racial disparities in delays starting PORT among white and AA HNSCC	PORT Delay
	TTP Initiation

Table 1. Study Objectives and Endpoints	
OBJECTIVES	ENDPOINTS
patients.	
To assess the preliminary clinical impact of NDURE compared with UC on barriers to care	Barriers Resolution Rate
	Unresolved barriers
To determine the preliminary clinical impact of NDURE compared with UC on cancer care delivery processes	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 evaluate the preliminary behavioral mechanism of action of NDURE	Care Transition Measure-15 (CTM-15) Score
	Change from Baseline in Interpersonal Support Evaluation List-12 Scale Score
	Change from Baseline in Perceived Susceptibility Scale Scores
	Change from Baseline in Illness Perception Questionnaire-Revised (IPQ-R) Consequences Sub-Scale Score
	Change in Baseline from Perceived Barriers Scale
	Change in Baseline from Communication & Attitudinal Self-Efficacy Scale (CASE)-Cancer Score

4 STUDY DESIGN

4.1 NDURE FEASIBILITY STUDY

4.1.1 OVERALL DESIGN

We will conduct a single-site, single-arm, non-blinded trial of NDURE to assess its feasibility and acceptability as an intervention to decrease delays and racial disparities starting PORT in adults with surgically-managed, locally advanced HNSCC (n=15; AA n=5; white n=10).

The study is designed to test the following hypotheses: 1) NDURE is feasible as measured by accrual rate, completion rate, and PN caseload; and 2) NDURE is acceptable, as measured by the Patient Satisfaction with the Interpersonal Relationship with the Navigator[30,31] and the Patient Satisfaction with Logistical Aspects of Navigation[32].

NDURE is feasible NDURE is a theory-based, multi-level PN intervention consisting of three 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 HNSCC care delivery, and improve clinical outcomes (timely, equitable PORT). NDURE will be delivered from surgical consultation to PORT initiation (~3 months). The three 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.

4.1.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

The single-arm study design was chosen to evaluate the feasibility and acceptability of the NDURE intervention. Questionnaires to be used in the RCT assessing symptom burden, interpersonal support, knowledge, and self-efficacy will be collected pre- and post-intervention to assess the feasibility of data collection procedures and monitor completion rates. Post-intervention, patients will complete validated measures of PN acceptability. Qualitative work with patients and providers will help refine NDURE. Our interdisciplinary team will consult with our scientific advisory board and community advocacy group to interpret the data about the feasibility and acceptability of NDURE to refine recruitment, retention, and the content, format, timing, and delivery of NDURE for the planned RCT. We considered other study designs that involve randomization. Although such a study design would allow us to evaluate feasibility of enrollment when there is a control group option (and thus reasons for study decline), it would dilute the sample size thereby minimizing the amount of information gained about feasibility of accrual to the intervention necessary before proceeding to the RCT. In addition, since the control group in the RCT is usual care, randomizing patients to usual in the feasibility and acceptability study would not add useful information about the acceptability of the control to the control group beyond what is already known from recent clinical experience in this setting.

4.1.3 END-OF-STUDY DEFINITION

The end of the study is defined relative to completion of the 3-month follow-up assessment shown in the Schedule of Activities (SoA), **Section 1.3**.

4.2 RCT OF NDURE VERSUS USUAL CARE

4.2.1 OVERALL DESIGN

We will conduct a single-site, non-blinded, parallel-group, RCT of NDURE versus usual care for the management of delays and racial disparities starting PORT in adults with surgically-managed, locally advanced HNSCC. The study is designed to test the following hypotheses: 1) NDURE will result in a lower rate of delayed PORT relative to usual care (primary objective) and 2) NDURE will result in a smaller difference in PORT delay between AA and whites relative to usual care (secondary objective). The statistical plan for this between-group design analyzes the superiority of NDURE relative to usual care, although our power analysis is calculated with $\alpha = 0.1$ and $1 - \beta = 0.8$ based on the desire to emphasize power over type I error at this early stage of development (single-site pilot RCT) to ensure follow-up on promising interventions.

Upon enrollment and completion of the baseline assessments, patients will be randomized 1:1 to NDURE or usual care using a permuted block randomization method, with randomly selected block sizes of 2 or 4. Randomization, which will occur at the individual patient level, will be stratified with a 1:1 allocation ratio with strata defined by race (white, AA) and location of radiation facility (MUSC, non-MUSC) because of the known association of these variables with PORT delay[6,33]. Furthermore, to facilitate evaluation of PORT delay rates in racial subgroups, we will oversample AAs for a final sample size of 50 white and 25 AA patients in each arm (see details **in Section 9.4.6, Sub-Group Analyses**). Given the impossibility of delivering the NDURE intervention in a non-blinded fashion, allocation concealment will be non-blinded. The study statistician (Hong Li, PhD) will generate the randomization schema and

randomization list. The study coordinator will implement the randomization. Randomization errors will be handled as per the modified intention-to-treat (ITT) population for the efficacy analysis.

NDURE is a theory-based, multi-level PN intervention consisting of three 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 HNSCC care delivery, and improve clinical outcomes (timely, equitable PORT). NDURE will be delivered from surgical consultation to PORT initiation (~3 months). The three 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.

In the RCT, NDURE will be compared with usual care. Usual care consists of clinic-based, provider-led discussion about the referrals needed to start PORT. Usual care was selected as the appropriate comparison group because it is the current standard for the population under study. Limitations of comparing NDURE to usual care (instead of active control) include the potential that improvements seen with NDURE (relative to usual care) are due to nonspecific effects. However, we are collecting data about the potential behavioral mechanisms underlying NDURE, which helps to limit the concern about non-specific effects of the NDURE intervention. In addition, given the pilot nature of this study, the goal is to achieve superior outcomes for patients over and above standard of care; therefore, usual care is a reasonable and appropriate comparison condition[34]. In the future, as we continue to assess and establish the efficacy of NDURE in larger trials, we will explore the 'active ingredients' relative to active control to better isolate the mechanisms underlying its efficacy.

Because of the pilot nature of the study, refining the NDURE intervention is critical to ensure that NDURE is optimally developed and delivered prior to future definitive efficacy testing. As such, we will conduct qualitative, semi-structured interviews on n=25 (20% of the subjects enrolled in NDURE [n=15] and n=10 providers) to assess perceived barriers and facilitators to NDURE delivery, qualitatively assess mechanisms of change, and optimize NDURE for future research.

4.2.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

We considered alternative study designs such as a single-arm pilot study with comparison to local and national historical control data. However, we consider the RCT a superior approach to a single-arm trial comparing to historical control[35] because the RCT will allow us to demonstrate and precisely measure the control group, thereby avoiding sample error and case-mix differences between the single-arm and historical control[36]. As a result, the RCT design will provide us with more precise estimates of the effect size and sample size of the NDURE intervention relative to usual care in preparation for the definitive phase III RCT[37]. Although methodological challenges (e.g. contamination)[38], will exist from running a single-site RCT (because providers will have patients in both NDURE and usual care concurrently), our group has experience successfully conducting single-site pilot RCTs[39,40]. Other groups testing PN have similarly reported successful study completion and avoidance of significant contamination when studying PN in the single-arm setting[10].

We also considered alternative comparison groups, including a form of active control against which to compare NDURE. Usual care is a more appropriate comparison group than active control because usual care represents the current standard for the management of this clinical scenario in population under study. Limitations of comparing NDURE to usual care (instead of active control) include the potential that improvements seen with NDURE (relative to usual care) are due to nonspecific effects instead of key 'active ingredients' within the NDURE intervention. However, a secondary objective of the trial is to

evaluate the preliminary behavioral mechanism of action of NDURE. As such, the data that we will analyze regarding underlying behavioral mechanisms will help to limit the concern about non-specific effects of the NDURE intervention. In addition, given the pilot nature of this trial, our goal is to achieve superior outcomes for patients over and above standard of care; therefore, usual care is a reasonable and appropriate comparison condition[34]. In the future, as we continue to assess and establish the efficacy of NDURE in larger trials, we will explore the 'active ingredients' relative to active control to better isolate the mechanisms underlying its efficacy.

4.2.3 JUSTIFICATION FOR INTERVENTION

4.2.3.1 JUSTIFICATION FOR THE MODE OF DELIVERY

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[10,25-27]. Although technology-enhanced interventions are increasingly common to facilitate care coordination, PN at its heart is still a patient-centered intervention and is delivered in person via face to face interactions. Face to face interactions can unduly burden patients and result in decreased intervention adherence. In addition, face to face interactions are being minimized to promote patient and healthcare worker safety during the COVID-19 pandemic.

The preferred method for delivering NDURE is face to face. However, due to changes in healthcare delivery necessitated by COVID-19 pandemic, it is permissible for the NDURE navigator to use a telemedicine videoconferencing platform for NDURE sessions 1 or 3 (study visit 2 or 4). The number, frequency, and timing of intervention contacts (see details **in Section 4.2.3.2, Justification for Number, Frequency, and Timing of Intervention Contacts**) were carefully chosen to minimize potential concerns that may arise from face to face interactions. In addition, supplemental contact beyond the three prescribed sessions will occur with a frequency and modality (e.g. text message, email, etc.) dictated by patient and navigator need.

4.2.3.2 JUSTIFICATION FOR NUMBER, FREQUENCY, AND TIMING OF INTERVENTION CONTACTS

The three NDURE sessions, which are expected to take 30-60 minutes each, will coincide with the presurgical consult, hospital discharge, and 1st postoperative clinic visit. These time points were chosen to facilitate case identification (preoperatively; Visit 2) and coordination across key care transitions from inpatient to outpatient status at the time of hospital discharge (inpatient; Visit 3) and from surgical to radiation and medical oncology specialties (post-discharge; Visit 4). These timepoints also promote the feasibility of NDURE delivery as nearly 100% of patients attend these three visits (despite travel distance-related barriers[41]) 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. The number of intervention contacts is justified by the need to focus the intervention to key transitions of care as described above.

4.2.4 END-OF-STUDY DEFINITION

The end-of-study is defined in relation to the 3-month follow-up (see **Section 1.3, Schedule of Activities [SoA]**). This end-of-study definition will permit sufficient follow-up to capture the primary endpoint, delays starting PORT (>6 weeks after surgery). A secondary endpoint, time-to-initiation of PORT (TTP), is defined as a continuous endpoint to measure the time from definitive surgery to the initiation of PORT.

As such, it is possible that at the conclusion of the **SoA**, a patient may not yet have initiated PORT (which would imply starting PORT more than 12 weeks after surgery). Based on national historical data, <9% of patients have such an extreme delay initiating PORT that they start more than 12 weeks after surgery[6]. Relative to the loss of marginal missing data that will require censoring for the TTP endpoint (which is secondary in nature), we believe that the cons of extending the end-of-study definition longer than what we have proposed in terms of the adverse impact on trial feasibility, grant funding timeline, and administrative loom large (as outweigh the pros). As such, we consider our end-of-trial definition justified.

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. Self-identified white or AA race
3. 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.
4. 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.
5. 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

6. 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
7. 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, N1 or greater 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. Synchronous untreated malignancy
   a. Patients with known untreated indolent malignancies (defined as non-melanoma skin cancer) at the time of diagnosis or that develop during the study period would not exclude a patient from the study
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, N1 or greater 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 $\geq$ 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 with 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 NDURE 2.0 trial will occur using a clinic-based approach from the MUSC Head and Neck Tumor Center, a high-volume academic HNSCC program at the NCI-designated Hollings Cancer Center. Research staff will use cancer center registry data, discussion with the HNSCC 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 HNSCC to participate in behavioral research during treatment periods. Recruitment is expected to be enhanced by the active clinical practice of the PI. The study participants may include patients of the PI's, but will not be exclusively patients of the PI. For potential participants where the PI is not the attending physician and the potential participant has not consented to participate in research per EPIC, the attending physician for the patient will introduce the study to the potential participant. Other than the notification of the study by the attending physician for potential trial participants, the research team will not ask other clinicians to be involved in recruitment. All of the recruitment will be handled by the study coordinator and team.

For the feasibility study, we propose to accrue 15 patients (white, n=10 and AA, n=5) to the study over 4 months. Based on data from MUSC/HCC for 2018, it is expected that 125 patients/year will be eligible for the study, of whom 22% are expected to be AA and 78% are expected to be white. During the 4-month accrual period, we would expect to screen 41 patients, of whom 9 would be AA and 32 would 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 60% of eligible patients will accrue to this study. Based on this 60% expected accrual rate, over the course of 4 months, we would expect to accrue our target of n=5 AA patients (and over-accrue white patients, n=20). Thus, by conservative estimates with over-sampling of AA, our accrual target for the AA subgroup (n=5) and overall (n=15) appear highly feasible.

For the RCT comparing NDURE to usual care, we note that our accrual rate target of 60%, by which we establish the feasibility of recruitment for this RCT, will have been tested in the pilot single-arm feasibility study. Refinements to the recruitment strategies and study timeline, as described below, will occur as needed to ensure that we achieve our accrual targets described below. We propose to accrue 75 patients to each arm (white, n=50 and AA, n=25) to the study over 36 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. During the 36-month accrual period, we would expect to screen 375 patients, of whom 83 would be AA and 292 would be white. Based on the PI and study team's prior experience recruiting and enrolling for similar studies embedded into clinical care and the feasibility data gathered from the single-arm pilot of NDURE, we anticipate that 60% of eligible patients will accrue to this study. Based on this 60% accrual rate, over the course of 36 months, we would expect to accrue 225 patients (50 AAs and 175 white). Thus, by conservative estimates with appropriate over-sampling of AAs, our overall accrual target (n=150) and for the AA racial subgroup (n=50) appear highly feasible. If continued optimization of enrollment and recruitment strategies fails to yield an accrual rate of 60%, we will extend the duration of the study accrual beyond the planned 36 months by an additional 6 months (and remain within the grant funding period). If we extend the study timeline for accrual by 6 months to 42 months instead of 36 months (and thus screen 437 patients [96

AAs] instead of 375 [83 AAs]), we would only need an accrual rate of 52% among AAs to achieve our racial subgroup distribution of n=50 (and an accrual rate of 29% among white HNSCC patients). For all of the above reasons (PI and team experience, feasibility testing, refinement of recruitment protocols, and extension of recruitment period), we are highly confident that we can accrue our overall and racial subgroup targets for the RCT.

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.

As a result of the aforementioned three strategies, retention of subjects is expected to be highly feasible. 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 HNSCC treatment is a significant strength and innovation of the study and will likely also improve retention relative to historical rates.

6 STUDY INTERVENTION

6.1 STUDY INTERVENTION ADMINISTRATION

6.1.1 STUDY INTERVENTION DESCRIPTION

6.1.1.1 NDURE

NDURE is a theory-based, multi-level PN intervention consisting of three 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 HNSCC care delivery, and improve clinical outcomes (timely, equitable PORT). The NDURE intervention components and targeted theoretical constructs are outlined in **Table 2**. NDURE will be delivered from surgical consultation to PORT initiation (~3 months). The three 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. The preferred method for delivering NDURE is face to face. However, due to changes in healthcare delivery necessitated by COVID-19 pandemic, it is permissible for the NDURE navigator to use a telemedicine videoconferencing platform for NDURE sessions 1 or 3 (study visit 2 or 4). Contact beyond the three prescribed sessions will occur with a frequency and modality (e.g. text message, email, etc.) dictated by patient and navigator need. During the first 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 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

Table 2. 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 HNSCC 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 HNSCC 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 HNSCC 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, HNSCC: Head and neck squamous cell carcinoma, PORT: Postoperative radiation therapy, SC: South Carolina

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.

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[42] is a critical determinant of cancer prevention, control, and treatment behaviors as well as cancer-related psychological and behavioral outcomes[43]. 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.

6.1.1.2 USUAL CARE

Usual care consists of clinic-based, provider-led discussion about the referrals needed to start PORT. Usual care is not formally theory-based. The targeted clinical endpoint is timely, Guideline-adherent adjuvant therapy.

6.1.2 ADMINISTRATION AND/OR DOSING

6.1.2.1 NDURE

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 navigation sessions (Study Visits 2-4), which are expected to take 30-60 minutes each. The NDURE sessions (Study Visits 2-4) will coincide with the presurgical consult, hospital discharge, and 1st postoperative clinic visit (see **Section 1.3, Schedule of Activities**). These time points were chosen to facilitate case identification and coordination across key care transitions. Contact beyond the three prescribed sessions will occur with a frequency and modality (e.g. text message, email, etc.) dictated by patient and navigator need. The NDURE intervention will delivered in the following settings: the MUSC Head and Neck Tumor Center and MUSC hospital. A single dedicated navigator with no competing clinical or administrative responsibilities outside of this trial will deliver the NDURE intervention. Full dose of the NDURE intervention will consist of completing all three navigation sessions. Because the administration schedule and dose of usual care is highly variable, the NDURE intervention will not be dose-matched to usual care on intensity, duration, and/or frequency. Participants in the trial are permitted to interact with other participants after randomization, regardless of treatment allocation. Such encounters may occur in waiting rooms before or after clinic appointments given the single-site design of the trial.

6.1.2.2 USUAL CARE

UC consists of discussions about the indications, risks/benefits/alternative, Guidelines, timing, and logistical details of adjuvant therapy. These discussions will be administered according to practice patterns of the involved providers. As such, usual care is expected to be variable in the number, frequency, intensity, and duration of visits and discussions dedicated to planning adjuvant therapy, depending upon the patient, provider, caregiver, tumor board, and clinical scenario. Usual care will be delivered in the following settings: the MUSC Head and Neck Tumor Center and MUSC hospital. No dedicated interventionist will deliver usual care; instead a combination of physicians (attendings and residents), nurse practitioners, and nurses from the relevant multidisciplinary specialties (surgical,

medical, radiation oncology) at MUSC or an outside facility will all contribute to these discussions. Administration of usual care will consist of direct face-to-face communication and other methods (e.g. telephone call, e-mail correspondence). The face-to-face conversations can occur during a structured clinical setting (e.g. clinic visit) or more informal, non-appointment-based manner (e.g. inpatient rounds). Given the variability in expected delivery of usual care, there is no number of sessions that constitute "full-dose". Because the administration schedule and dose of usual care is highly variable, usual care will not be dose-matched to NDURE on intensity, duration, and/or frequency. However, the three clinical encounters at which NDURE will be delivered are clinical in nature and thus will likely correlate highly with usual care. Participants in the trial are permitted to interact with other participants after randomization, regardless of treatment allocation. Such encounters may occur in waiting rooms before or after clinic appointments given the single-site design of the trial.

6.2 FIDELITY

6.2.1 INTERVENTIONIST TRAINING AND TRACKING

Because the objectives of the protocol depend upon consistent administration of the NDURE intervention, the fidelity of delivery will be monitored closely. The specific duties necessary to ensure optimal administration of NDURE are detailed in the NDURE Navigator Standard Operating Procedure (SOP). 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)[44]. 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

Bias will be minimized through stratified sampling and a stratified randomized permuted block design. We will use a stratified sampling approach to achieve a fixed sample size for AA patients (n=25 in each arm) to ensure that we 1) achieve racial balance between the NDURE and UC arms, and 2) oversample AA relative to their frequency in the study population. Oversampling AAs is key for the study design because of the prognostic significance of AA race with delayed PORT initiation[6,33]. We will then use a stratified randomization scheme, with randomization at the individual patient level using a 1:1 allocation ratio. Strata will be defined by location of radiation facility (MUSC, non-MUSC) because of the known association of this variable with PORT delay[6,33]. As such, our design balances by key potential confounders across trial arms. Patients will be randomized 1:1 to NDURE or usual care using a permuted block randomization method, with randomly selected block sizes of 2 or 4. Given the impossibility of delivering the NDURE intervention in a non-blinded fashion, allocation concealment will be non-blinded. The study statistician (Hong Li, PhD) will generate and implement the randomization schema and randomization list. The study coordinator will implement the randomization. Randomization errors will be handled as per the modified ITT population for the efficacy analysis (see **Section 9.3, Population for Analyses**).

6.4 STUDY INTERVENTION/EXPERIMENTAL MANIPULATION ADHERENCE

Participants' adherence with study procedures will be tracked by attendance at intervention visits. All study visits are mandatory to remain an active participant. Adherence to attendance at Visits 2-4 will be ascertained from the NDURE visit note authored by the navigator that is available in the EMR. Adherence to attendance at Visits 1 and 5 will be ascertained from the REDCap data collection form. Adherence to attendance at visits 1-5 will be documented in the electronic Case Report Form (eCRF).

6.5 CONCOMITANT THERAPY

N/A

6.5.1 RESCUE THERAPY

N/A

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION/EXPERIMENTAL MANIPULATION

At subject, PI, or study team member request.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants are free to withdraw from participation in the study at any time upon request. The investigators will seek to minimize participant discontinuation/withdrawal from the study (see **Section 7.3, Lost to Follow-Up**) except for safety reasons.

The investigator may discontinue a participant from the study for the following reasons:

- Significant study intervention non-compliance
- 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. Specific situations in which this is expected to occur through the course of the study are:
    1) Patient is expected to have surgery and then decides to pursue a nonsurgical treatment (thus not undergoing curative-intent surgery at MUSC)
    2) Patient is expected to have surgery at MUSC and then decides to pursue treatment elsewhere (thus not undergoing curative-intent surgery at MUSC)
    3) PORT is expected based on the clinical TNM classification, but analysis of the pathology specimen after surgery demonstrates no indication for PORT (with or without concurrent chemotherapy) per NCCN Guidelines based on the absence of all of the following adverse features: ENE, positive margin, pT3 or pT4 primary, N1 or greater nodal disease, nodal disease in levels IV or V, PNI, or LVI

The reason for participant discontinuation or withdrawal from the study will be recorded on the eCRF. Subjects who sign the informed consent form and are randomized but do not receive the study intervention may be replaced. Subjects who sign the informed consent form, and are randomized and receive the study intervention, and subsequently withdraw, will not be replaced. Subjects sign the informed consent form, are randomized and receive at least some of the study intervention and are subsequently found to meet one of the exclusion criteria 1-3 described above, will be replaced.

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 ASSESSMENT

Feasibility

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

NDURE Completion Rate is defined as the proportion of enrolled patients who complete the baseline assessment, at least two NDURE intervention sessions, and the final follow-up assessment

Navigation Session Completion Rate is the proportion of NDURE navigation sessions completed by each individual

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 PORT

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

Questionnaire Completion Rate is the proportion of pre- and post-treatment questionnaires completed by enrolled patients

Acceptability

Satisfaction with the Interpersonal Relationship with the Navigator Scale Score is defined as the total score of this 9-item measure of the satisfaction of the interpersonal relationship with the patient navigator. This reliable and validated measure[30,31] has been widely used in prior studies of PN. The total score of the measure ranges from 9 (minimum) to 45 (maximum); higher scores represent a better outcome (greater satisfaction with the interpersonal relationship with the navigator).

Satisfaction with Logistical Aspects of Navigation Scale Score is defined as the total score of the 26-item measure of the satisfaction of the logistical aspects of PN. This reliable and validated measure[32] has been widely used in prior studies of PN. The total score of the measure ranges from 0 (minimum) to 78 (maximum); higher scores represent a better outcome (greater satisfaction with the logistical aspects of navigation).

Clinical Outcomes

PORT Delay is defined as the initiation of PORT more than 6 weeks (42 calendar days) from the date of the definitive surgical resection. 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 definitive 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 date of definitive surgical resection.

Time-to-PORT (TTP) is defined as the time, in days, between the date of definitive surgical resection to the initiation of PORT. 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 to Care

Rate of barrier resolution is defined as the proportion of confirmed barriers (as determined by the navigator log) that are resolved during the NDURE intervention.

Unresolved barriers are the number of confirmed barriers (as determined by the navigator log) that are not resolved during the NDURE intervention.

Cancer Care Delivery Processes

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 HNSCC 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.

Health Behavior Constructs

Care Transition Measure-15 (CTM-15) score is reported as a score out of 100 and calculated as the mean score (the summed score from each question divided by the total number of questions) with a linear transformation to 100. The 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[45]. Items are rated on a 4-point Likert scale from ‘Strongly Disagree’ (1) to ‘Strongly Agree’ (4). Higher scores reflect more care integration and better care transitions.

Change from baseline in Interpersonal Support Evaluation List-12 (ISEL-12) score is defined as the change in total ISEL-12 scores from baseline. The ISEL-12 is a validated, 12-item assessment of three subscales (appraisal, belonging, and tangible)[46] that has been used to assess support in prior PN studies[47]. Items are rated on a 4-point Likert scale from 'Definitely False' (1) to 'Definitely True' (4). The score is calculated by summing scores across all items (with reverse coding for items 1, 2, 7, 8, 11, 12). Scores range from 12-48. Higher scores indicate more support.

Change from baseline in Perceived Susceptibility Questionnaire score is defined as the change in the score for each of the two subscales relative to baseline. The Perceived Susceptibility Questionnaire is a validated 3-item perceived susceptibility subscale for mammography screening[48] that has been modified to assess perceived susceptibility for delays starting PORT after HNSCC surgery. It consists of two subscales. The first subscale consists of two questions, one assessing absolute perceived susceptibility to delays starting PORT and the other assessing relative perceived susceptibility to delays starting PORT. Items are rated on a 5-point Likert scale from 'Strongly Disagree' (1) to 'Strongly Agree' (5). The score of the subscale is calculated by summing scores across all items. Total scores for the subscale range from 2-10. Higher scores indicate greater perceived susceptibility to delays starting PORT. The second subscale is a single item assessing the cognitive evaluation of absolute perceived susceptibility to PORT delay. The item is measured as a continuous measure from 0 (no chance of delay) to 100 (guaranteed delay). Scores on this subscale range from 0-100 with higher scores indicating a greater perceived susceptibility to PORT delays.

Change from baseline in Illness Perception Questionnaire-Revised (IPQ-R) Consequences Subscale (HNSCC Modification) score is defined as the change in IPQ-R Consequences Subscale Score from baseline. The IPQ-R is a validated assessment of a patient's self-representation of the health consequences of their illness that consists of 8 separate subscales[49]. The IPQ-R Consequences Subscale is easily modifiable to asses disease-specific perceived severity[50].The HNSCC Modification of the IPQ-R Consequences Subscale consists of 6 questions. Items are rated using a 5-point Likert scale from 'Strongly Disagree' (1) to 'Strongly Agree' (5). The score is calculated by summing across all items (with reverse coding for item 3). Scores range from 5 to 30. Higher scores indicate a greater degree of perceived severity of the illness.

Change from baseline in 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[11,44,51,52].

Change from baseline in Communication & Attitudinal Self-Efficacy Scale (CASE)-Cancer score is defined as the change in CASE-Cancer Score from baseline. The 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)[53]. The CASE-Cancer scale has been used extensively in PN studies to measure perceived self-efficacy[10,44,52]. Responses are on a 4-point Likert scale from 'Strongly disagree' (1) to 'Strongly Agree' (4). Higher scores indicate greater levels of self-efficacy in cancer care.

Navigator Barrier Log 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[11,44,51]

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[54].

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 ≥ 5 drinks, and maximum number of drinks.

Clinical and Oncologic Characteristics. Clinical characteristics will include comorbid medical conditions (as defined by the ACE-27[55], which ranks the severity of each of a patient's comorbidities from 0-3 and gives an overall comorbidity score based on the patient's highest comorbidity score for any individual type of ailment, with 3 indicating severe comorbidity) and cancer history. Oncologic characteristics will include HNSCC tumor subsite, HNSCC 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).

Cultural Factor Survey Scores is reported as the total score for each of the three individual subscales. The 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)[56]. Prior PN studies have used these scales to measure cultural factors[57]. Items are scored on a 4-point Likert scale from 'Strongly Disagree' (1) to 'Strongly Agree' (4). Scores on each sub-scale range from 5-20 (temporal orientation), 6-24 (collectivism), and 9-36 (religiosity). Higher scores on each subscale indicate greater amounts of each of the measured construct.

PORT Nomogram is a validated risk-prediction tool to estimate a personalized pre-treatment risk of PORT delay[58].

8.2 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.2.1 DEFINITION OF ADVERSE EVENTS

This trial is considered to carry a low risk to subjects (i.e. has a "no more than minimal risk" designation). As such, this protocol defines an adverse event (AE) as any undesirable sign, symptom, medical, psychological, social, or emotional reaction that is definitely, probably, or possibly related to the study intervention.

8.2.2 DEFINITION OF SERIOUS ADVERSE EVENTS

A serious adverse event (SAE) will be considered any undesirable sign, symptom, or medical condition which is fatal, is life-threatening, requires or prolongs inpatient hospitalization, results in persistent or significant disability/incapacity, constitutes a congenital anomaly or birth defect, is medically significant and which the investigator regards as serious based on appropriate medical judgment. An important medical event is any AE that may not result in death, be life-threatening, or require hospitalization but may be considered an SAE when, based upon appropriate medical judgment, it may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in the definitions of SAEs.

8.2.3 CLASSIFICATION OF AN ADVERSE EVENT

8.2.3.1 SEVERITY OF EVENT

The following guidelines will be used to describe AE severity.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".

8.2.3.2 RELATIONSHIP TO STUDY INTERVENTION

All AEs will have their relationship to study procedures, including the intervention, assessed by the PI based on temporal relationship and his clinical judgment. The degree of certainty about causality will be graded using the categories below.

- **Definitely Related** – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to study procedures administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the study procedures should be clinically plausible. The event must be pharmacologically or phenomenologically definitive.
- **Probably Related** – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the study procedures, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal.
- **Possibly Related** – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of study procedures). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.

8.2.3.3 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

Recording/reporting of AEs will begin after the subject signs informed consent and end after the subject completes the intervention and follow up period as defined in the protocol.

8.2.3.4 ADVERSE EVENT REPORTING

All AEs, as defined above, will be collected and reported. Data collection will occur via electronic spreadsheet. The information will be saved in REDCap and managed by the study team. In consultation with the PI, a trained member of the study team will be responsible for conducting an evaluation of a SAE and shall report the results of such evaluation to the NIH and the reviewing Institutional Review Board (IRB) as soon as possible and in accordance with the reviewing IRB policy

8.2.3.5 SERIOUS ADVERSE EVENT REPORTING

In consultation with the PI, a trained member of the study team will be responsible for conducting an evaluation of a SAE and shall report the results of such evaluation to the NIH and the reviewing IRB as soon as possible and in accordance with the reviewing IRB policy.

8.2.3.6 REPORTING EVENTS TO PARTICIPANT

N/A

8.2.3.7 EVENTS OF SPECIAL INTEREST

N/A

8.2.3.8 REPORTING OF PREGNANCY

N/A

8.3 UNANTICIPATED PROBLEMS

8.3.1 DEFINITION OF UNANTICIPATED PROBLEMS

This protocol uses the definition of Unanticipated Problems (UP) as defined by the Office for Human Research Protections (OHRP). OHRP considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

8.3.2 UNANTICIPATED PROBLEMS REPORTING

The investigator will report UPs to the reviewing IRB and to the lead PI. The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number
- A detailed description of the event, incident, experience, or outcome
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- Ups will be reported to the IRB and to the NCI in accordance with policy regarding timeliness of reporting

- All UPs should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and the OHRP in accordance with policy regarding timeliness

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

- Primary Endpoint:

PORT Delay

We hypothesize that, compared with patients who receive usual care, patients who receive NDURE will have a decreased rate of PORT delay (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 NDURE and usual care.

The preliminary efficacy analysis will be calculated for the primary endpoint over the 6 week time period from the date of definitive surgical resection of the primary tumor.

- Secondary Endpoints:

PORT Delay

We hypothesize that, compared with usual care, NDURE will result in a smaller difference in the rate of PORT delay (initiation of PORT > 6 weeks after surgery) between AA and white patients. Alternatively, our null hypothesis is that there will be no difference in the rate of PORT delay between AA and white patients between NDURE and usual care.

The preliminary efficacy analysis will be calculated for the primary endpoint over the 6 week time period from the date of definitive surgical resection of the primary tumor.

TTP

We hypothesize that, compared with patients who receive usual care, patients who receive NDURE will have a shorter median TTP (time, in days, between the date of definitive surgical resection to the initiation of PORT). Alternatively, our null hypothesis is that there will be no difference in median TTP between NDURE and usual care.

TTP

We hypothesize that, compared with usual care, NDURE will result in a smaller difference in the median TTP between AA and white patients. Alternatively, our null hypothesis is that there will be no difference in the median TTP between AA and white patients between NDURE and usual care.

NDURE Accrual

We hypothesize that at least 60% of eligible subjects for the NDURE study will accrue to the study. Alternatively, our null hypothesis is that less than 60% of eligible subjects for the NDURE study will accrue to the study

The preliminary feasibility analysis will be calculated for the secondary endpoint using the first 25 patients eligible to accrue to the study, which is expected to occur over 4 months.

NDURE Completion

We hypothesize that at least 85% of subjects who enroll in the NDURE study (at least 13 of 15 subjects) will complete all 3 NDURE sessions. Alternatively, our null hypothesis is that less than 13 of the 15 subjects who enroll in the NDURE study will complete all 3 NDURE sessions

The preliminary feasibility analysis will be calculated for the secondary endpoint using the first 15 patients who accrue to the study, which is expected to occur over 6 months.

9.2 SAMPLE SIZE DETERMINATION

9.2.1 NDURE FEASIBILITY STUDY

Power and sample size calculations were performed using the University of Iowa Binomial Distribution applet. The sample size justification for this single-arm study is based on the primary feasibility endpoints of NDURE accrual and completion. In the RCT of NDURE, we plan to enroll 60% of eligible patients. We expect similar accrual in this feasibility study. Therefore, we hypothesize that at least 60% of eligible subjects for the NDURE study will accrue to the study. Alternatively, our null hypothesis is that less than 60% of eligible subjects for the NDURE study will accrue to the study. Accruing to NDURE will be considered feasible if at least 15 of 25 eligible subjects enroll. Our sample size for the feasibility study was selected to provide a small probability of having an observed accrual rate of at least 60% when the true accrual probability is actually less than 60%. For example, if the true accrual probability for our proposed design is 45% (35%), the probability of enrolling 15 or more of 25 eligible subjects is only 10% (1%). Additionally, we hypothesize that at least 85% of subjects who enroll in the NDURE study will complete all 3 NDURE sessions. Alternatively, our null hypothesis is that less than 85% of subjects who enroll in the NDURE study will complete all 3 NDURE sessions That is to say, NDURE will be considered feasible if at least 13 of the 15 subjects enrolled complete all three NDURE sessions. Accordingly, our sample size for the single-arm study was selected to provide a small probability of having an observed completion rate of at least 85% when the true completion probability of the intervention is actually less than 85%. For example, if the true completion probability for our proposed design is 70% (60%), the probability that 13 or more of the 15 enrolled patients complete all three NDURE sessions is 13% (3%). Therefore, the probability of falsely declaring NDURE feasible is reasonably controlled based on this sample size.

9.2.2 RCT OF NDURE VERSUS USUAL CARE

Power and sample size calculations were performed using PASS v08.0.13, “Inequality Tests for Two Independent Proportions.” The primary endpoint for this pilot RCT is the rate of PORT delay, defined as starting PORT > 6 weeks after surgery. Our primary objective is to compare PORT delay rates between the NDURE and usual care arms. We hypothesize that, compared with patients who receive usual care, patients who receive NDURE will have a decreased rate of PORT delay (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 NDURE and usual care. We assume the rate of PORT delay in the usual care arm will be 45%[33] and target an absolute reduction in PORT delay of 20% (rate of PORT delay in the NDURE arm = 25%)[24]. This effect size is clinically significant and realistic given results in similar (non-randomized) interventions[24]. Seventy-five patients in each arm yields 83% power to detect a 20% reduction in PORT delay (45% versus 25%) based on a two-sided Mantel-Haenszel test of two independent proportions assuming a two-sided $\alpha = 0.1$. Our choice of the Mantel-Haenszel test to compare proportions is based on the trial’s stratified design. Our selection of $\alpha = 0.1$ and $1 - \beta = 0.8$ is based on the desire to emphasize power over type I error at this early stage of development (single-site pilot RCT) to ensure follow-up on promising interventions. We therefore consider our RCT to be appropriately and rigorously designed to detect a clinically meaningful reduction in PORT delay. In order to have 150 patients eligible for the

efficacy analysis in the modified ITT population (see **Section 9.3, Population for Analyses**), we plan to enroll 170 patients. Our sample size is inflated by 17% based on historical data. This inflation account for the predictable subset of patients would be enrolled in the study, be randomized to NDURE or Usual Care, receive a portion of the intervention (NDURE Visit 1) and then subsequently develop a study exclusion criterion, namely: 1) failure to undergo curative intent surgery at MUSC (exclusion criteria #4); 2) 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.

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, pilot RCT).

We note that our accrual rate target of 60%, by which we establish the feasibility of recruitment for this RCT, will have been tested in the feasibility study as described. Refinements to the recruitment strategies and study timeline will occur as needed to ensure that we achieve our accrual targets described below. We propose to accrue 75 patients to each arm (white, n=50 and African American, n=25) to the study over 36 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 African American and 97 (78%) are expected to be white. During the 36-month accrual period, we would expect to screen 375 patients, of whom 83 would be African American and 292 would be white. Based on the PI and study team's prior experience recruiting and enrolling for similar studies embedded into clinical care and the feasibility data gathered from the single-arm pilot of NDURE, we anticipate that 60% of eligible patients will accrue to this study. Based on this 60% accrual rate, over the course of 36 months, we would expect to accrue 225 patients (50 African Americans and 175 white). Thus, by conservative estimates with appropriate over-sampling of African Americans, our overall accrual target (n=150) and for the African American racial subgroup (n=50) appear highly feasible. If continued optimization of enrollment and recruitment strategies fails to yield an accrual rate of 60%, we will extend the duration of the study accrual beyond the planned 36 months by an additional 6 months (and remain within the grant funding period). If we extend the study timeline for accrual by 6 months to 42 months instead of 36 months (and thus screen 437 patients [96 African Americans] instead of 375 [83 African Americans]), we would only need an accrual rate of 52% among African Americans to achieve our racial subgroup distribution of n=50 (and an accrual rate of 29% among white HNSCC patients). For all of the above reasons (PI and team experience, prior feasibility testing, refinement of recruitment protocols, and extension of recruitment period), we are highly confident that we can accrue our overall and racial subgroup targets for the RCT.

9.3 POPULATIONS FOR ANALYSES

For the efficacy analysis, we will utilize a modified 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, at least pN1 nodal disease (per AJCC 8th edition for p16-ve

non-oropharyngeal SCC or AJCC 7th edition for p16+ve oropharyngeal SCC), nodal disease in levels IV or V, PNI or LVI

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). Therefore, 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). Covariates will be pre-specified as described below. 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

9.4.2.1 NDURE FEASIBILITY STUDY

For the primary endpoint (NDURE Accrual Rate), we will calculate the proportion and frequency of eligible patients who accrue (overall, white, and African American). Given its pilot nature, the study is not designed to evaluate racial differences in accrual, although reasons for study decline will be collected, analyzed for each racial subgroup, and used to refine recruitment.

9.4.2.2 RCT OF NDURE VERSUS USUAL CARE

For the primary endpoint (delays starting PORT as defined in **Section 8.1, Endpoint and Other Non-Safety Assessments**), we will calculate the percentage of patients who start PORT > 6 weeks after surgery and corresponding 95% confidence interval (CI) for both arms and for white and AA subgroups within each arm in the efficacy analysis population. The rate of PORT delay will be compared between arms using a Mantel-Haenszel test of two proportions, with strata defined by race and location of radiation facility.
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.

9.4.3 ANALYSIS OF THE SECONDARY ENDPOINTS

9.4.3.1 NDURE FEASIBILITY STUDY

NDURE completion rate will be analyzed as 1) the percentage of enrolled patients who attend all three NDURE sessions and 2) the proportion of three 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 will be summarized as described above for continuous data. Study questionnaire completion rate will be calculated as the proportion of pre- and post-intervention questionnaires (n=5 each) completed. Qualitative data will be analyzed using established team codebooks and focus on the content, format, delivery, and timing of NDURE. Qualitative analysis of semi-structured interviews with patients and providers following the pilot will be analyzed using established codebooks from the study team for evaluating the feasibility and acceptability of clinic-based HNSCC interventions with a focus on the content, format, delivery, and timing of NDURE.

9.4.3.2 RCT OF NDURE VERSUS USUAL CARE

We will analyze the secondary endpoint of TTP as a continuous variable and estimate median time to PORT for each arm and for racial subgroups within each arm using Kaplan-Meier curves with Greenwood variance estimation to construct the corresponding 95% CIs. Hazard ratio comparing the two arms will be estimated using Cox proportional hazards regression controlling for the stratification variables. TTP will be compared between intervention arms using a stratified log-rank test on the modified ITT efficacy analysis population.

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[51]. 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.**

For other secondary endpoints, data will be summarized using frequency and percent for categorical variables and using mean, median, standard deviation, IQR and range for continuous variables. We will construct 95% CIs to provide a measure of uncertainty in estimated proportions and means. Comparisons between trial arms of other secondary endpoints will be performed using *t*-tests and chi-square tests, or Wilcoxon rank sum and Fisher's exact tests as appropriate. Pre- and post-intervention values of variables measuring the theoretical constructs underlying NDURE (i.e. care coordination, self-efficacy in cancer care, support, and knowledge) will be compared using Wilcoxon sign rank tests. Comparisons between arms of the change in scores will be conducted using Wilcoxon rank sum tests. All secondary endpoint

will be analyzed on the modified ITT efficacy analysis population. Missing data will be handled as described in **Section 9.4.2.2, RCT of NDURE Versus Usual Care.**

9.4.4 BASELINE DESCRIPTIVE STATISTICS

Baseline characteristics (e.g., demographics, oncologic details, behavioral characteristics) for the NDURE and Usual Care arms will be compared and descriptive statistics calculated. Baseline differences between the two groups, stratified by race and location of radiation facility, will be compared using t-tests and chi-square tests, or Wilcoxon rank sum and Fisher's exact tests as appropriate.

9.4.5 PLANNED INTERIM ANALYSES

N/A

9.4.6 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 biologic variables. 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.

9.4.7 TABULATION OF INDIVIDUAL PARTICIPANT DATA

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

9.4.8 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 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, DSMB).

10.1.3 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, the safety and oversight monitor(s), and the sponsor(s) and funding agency. This confidentiality is extended to the data being collected as part of this study. Data that could be used to identify a specific study participant will be held in strict confidence within the research team. No personally identifiable information from the study will be released to any unauthorized third party without prior written approval of the sponsor/funding agency. 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.
All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the sponsor or funding agency, representatives of the IRB, regulatory agencies or representatives from companies or organizations supplying the product, may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor/funding agency requirements.

It is NIH policy that the results and accomplishments of the activities that it funds should be made available to the public (see *https://grants.nih.gov/policy/sharing.htm*). The PI will ensure all mechanisms used to share data will include proper plans and safeguards for the protection of privacy, confidentiality, and security for data dissemination and reuse (e.g., all data will be thoroughly de-identified and will not be traceable to a specific study participant). Plans for archiving and long-term preservation of the data will be implemented, as appropriate.

To further protect the privacy of study participants, the Secretary, Health and Human Services (HHS), has issued a Certificate of Confidentiality (CoC) to all researchers engaged in biomedical, behavioral, clinical or other human subjects research funded wholly or in part by the federal government. Recipients of NIH funding for human subjects research are required to protect identifiable research information from forced disclosure per the terms of the NIH Policy (see *https://humansubjects.nih.gov/coc/index*). As set forth in 45 CFR Part 75.303(a) and NIHGPS Chapter 8.3, recipients conducting NIH-supported research covered by this Policy are required to establish and maintain effective internal controls (e.g., policies and procedures) that provide reasonable assurance that the award is managed in compliance with Federal statutes, regulations, and the terms and conditions of award. It is the NIH policy that investigators and others who have access to research records will not disclose identifying information except when the participant consents or in certain instances when federal, state, or local law or regulation requires disclosure. NIH expects investigators to inform research participants of the protections and the limits to protections provided by a Certificate issued by this Policy.

10.1.4 FUTURE USE OF STORED SPECIMENS AND DATA

Data collected for this study will be analyzed and stored with the study team. After the study is completed, the de-identified, archived data will be transmitted to and stored with the study team, for use by other researchers including those outside of the study.

10.1.5 KEY ROLES AND STUDY GOVERNANCE

Principal Investigator
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10.1.6 SAFETY OVERSIGHT

Safety oversight will be under the direction of a PI. 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 (QA) AND QUALITY CONTROL (QC)
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 eCRF derived from source documents will be consistent with the data recorded on the source documents.

Clinical data 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 PROTOCOL DEVIATIONS

A protocol deviation is any variance from the protocol involving a subject or subjects that is not approved by the IRB prior to its initiation or implementation, and occurs when a member of the study team departs from the IRB-approved protocol in any way without the investigator first obtaining IRB approval (See MUSC IRB Policy HRPP 4.14).

10.1.11 PUBLICATION AND DATA SHARING POLICY

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

National Institutes of Health (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 2 years after the completion of the primary endpoint by contacting Evan Graboyes, MD. Considerations for ensuring confidentiality of these shared data are described in **Section 10.1.3.**

10.1.12 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership in conjunction with the NCI has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

10.2 ADDITIONAL CONSIDERATIONS

N/A

10.3 ABBREVIATIONS AND SPECIAL TERMS

Table 3. Abbreviations and Special Terms	
AA	AA
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
eCRF	Electronic Case Report Form
CT	Computed Tomography
CTM-15	Care Transition Method-15
DCC	Data Coordinating Center
DSMB	Data Safety Monitoring Board
eCRF	Electronic Case Report Forms
EMR	Electronic Medical Record
ENE	Extranodal Extension
FDA	Food and Drug Administration
FDG	Fluoro-deoxyglucose
GCP	Good Clinical Practice
HBM	Health Belief Model
HCC	Hollings Cancer Center
HIPAA	Health Insurance Portability and Accountability Act
HNSCC	Head and Neck Squamous Cell Carcinoma
ICH	International Council on Harmonisation
IDE	Investigational Device Exemption
IND	Investigational New Drug
IPQ-R	Illness Perception Questionnaire-Revised
IRB	Institutional Review Board
ISEL-12	Interpersonal Support Evaluation List-12
ITT	Intention-To-Treat
LVI	Lymphovascular Invasion
MOP	Manual of Procedures
MRI	Magnetic Resonance Imaging
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
PET	Positron Emission Tomography
PI	Principal Investigator
PN	Patient Navigation
PNI	Perineural Invasion
PORT	Postoperative Radiation Therapy
QA	Quality Assurance
QC	Quality Control
RCT	Randomized Controlled Trial
REDCap	Research Electronic Data Capture
RT	Radiation Therapy
SCC	Squamous Cell Carcinoma
SAE	Serious Adverse Event
SoA	Schedule of Activities
SOP	Standard Operating Procedure

TTP	Time-to-PORT
UP	Unanticipated Problem
US	United States

10.4 PROTOCOL AMENDMENT HISTORY

Table 4. Protocol Amendment History

Version	Date	Description of Change	Brief Rationale
1.1	7/26/19	-Removed 10th floor from location of ICF process -removed language about ability to provide informed consent and adhere to study regimen from inclusion criteria	-changes requested by MUSC IRB
2.0	9/27/19	-updated objectives to specify comparison of NDURE with UC -created more comprehensive and specific SoA -removed neoadjuvant therapy; added synchronous malignancy to exclusion criteria -removed MDASI-HN -added NIH confidentiality vocab	-enhance clarity of objectives -more transparent SoA -improve clinical relevance of target population -improve clinical workflow -NIH compliance
3.0	12/16/19	-replaced Elizabeth Hill with Hong Li on study team -updated SOA -added white or AA race to inclusion criteria -clarified stratified sampling and stratified randomization -rename barrier load survey -harmonized staging information in inclusion criteria with mod ITT population	-Elizabeth Hill left MUSC/HCC -more precision; address accidental overlap between visit 1 and 2 -internally harmonize protocol -previously mis-reported as stratified randomization across two strata -clarity for study assessment -internally harmonize protocol
4.0	2/26/20	-allowed use of telemedicine for NDURE sessions 1 or 3 -added NDURE nomogram -clarified that comorbidity will be measured using ACE-27	-COVID-19 -assess pre-treatment risk of PORT delay -previously not specified

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