A Single-Site, Parallel-Group, Randomized-Controlled Pilot Trial Comparing BRIGHT with Active Control in Reducing Body Image Disturbance Among Head and Neck Cancer Survivors (BRIGHT 2.0)

Protocol Number: 103191

National Clinical Trial (NCT) Identified Number: NCT03831100

Principal Investigator: Evan Graboyes, M.D., M.P.H., FACS

Sponsor: Hollings Cancer Center

Grant Title: A Novel Treatment Strategy for Body Image Disturbance in Head and Neck Cancer Survivors

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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 Acceptance of this document constitutes agreement by the recipient that no unpublished information contained herein will be published or disclosed without prior approval of the Principal Investigator or other participating study leadership and as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 5.2 Exclusion Criteria: Removed "exclusion criteria" of (1) recurrent/new primary cancer following trial registration and (2) major surgery following trial registration. These criteria were incorrectly listed as exclusion criteria even though their determination occurred after a patient was enrolled (and thus they cannot, by definition, be exclusion criteria).

Section 5.5 Strategies for Recruitment and Retention: Changed target accrual from 48 to 52 patients to reflect a higher than anticipated rate of patients discontinuing the study due to recurrent or second primary cancers (**Section 7.2**). The evaluable sample size remains unchanged (N=44).

Section 7.2 Participant Discontinuation/Withdrawal from the Study: Refined criteria for study discontinuation to clarify the difference between an exclusion criterion (which is determined at the time of study accrual) and criteria for study discontinuation (which are determined after a patient accrues to the study). The criteria (recurrence or second primary cancer; major head and neck surgery) and rationale (these events/.medical conditions are such that continued f/u of the patient in the study is not in the participant's best interest and would confound interpretation of the study) remain the same but are now appropriately described as criteria for discontinuation instead of exclusion criteria.

Section 9.2 Sample Size Determination: Changed target accrual from 48 to 52 patients to reflect a higher than anticipated rate of patients discontinuing the study due to recurrent or second primary cancers (**Section 7.2**). The evaluable sample size remains unchanged (N=44).

Section 9.3 Population for Analyses: Amended to reflect updates to eligible vs evaluable population as described in **Sections 5.2** and **7.2**

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

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STATEMENT OF COMPLIANCE

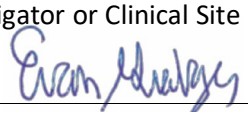
The trial will be conducted in accordance with International Council on Harmonisation Good Clinical Practice (ICH GCP), applicable United States (US) Code of Federal Regulations (CFR), and the National Cancer Institute (NCI) Terms and Conditions of Award. The Principal Investigator (PI) will assure that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

Signed:  Date: 3/10/20

Name: Evan Graboyes
Title: A Single-Site, Parallel-Group, Randomized-Controlled Pilot Trial Comparing BRIGHT with Active Control in Reducing Body Image Disturbance Among Head and Neck Cancer Survivors (BRIGHT 2.0)

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

CO-INVESTIGATORS:
Stacey Maurer, PhD
Wendy Balliet, PhD
Hong Li, PhD
Ken Ruggiero, PhD
Katherine Sterba, PhD, MPH

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title: A Single-Site, Parallel-Group, Randomized-Controlled Pilot Trial Comparing BRIGHT with Active Control in Reducing Body Image Disturbance Among Head and Neck Cancer Survivors (BRIGHT 2.0)

Grant Number: R21CA245941

Study Description: In this pilot randomized controlled trial, we will evaluate the preliminary clinical impact and underlying behavioral mechanism of BRIGHT (Building a Renewed ImaGe after Head & neck cancer Treatment), a novel 5-session, manualized cognitive behavioral therapy (CBT) intervention to treat body image disturbance (BID) in head and neck cancer (HNC) survivors. We hypothesize that BRIGHT will decrease BID relative to active control (AC; patient-centered videos about HNC survivorship care) through improvements in body image coping behavior.

Objectives:

Primary Objective:
To assess the clinical efficacy of BRIGHT compared with AC on BID in HNC survivors as determined by change in Body Image Scale (BIS) scores at 1-month post-intervention relative to baseline.

Select Secondary Objectives:
1. To assess the clinical efficacy of BRIGHT compared with AC on BID in HNC survivors as determined by change in IMAGE-HN scores at 1-month post-intervention relative to baseline

2. To explore the behavioral mechanism of action of BRIGHT on changes in BID in HNC survivors as measured by the change in Body Image Coping Strategies Inventory (BICSI) scores at 1-week post-intervention relative to baseline.

3. To provide preliminary estimates of the clinical effect of AC on BID in HNC survivors as determined by change in BIS scores at 1-month post-intervention.

4. To estimate the activity of BRIGHT compared with AC on BID in HNC survivors in terms of clinical response as measured by improvement in BIS scores at 1-month post-intervention relative to baseline.

5. To assess the clinical efficacy of BRIGHT compared with AC on BID in HNC survivors as determined by change in BIS scores at 3-months post-intervention relative to baseline.

	6. To evaluate the preliminary clinical efficacy of BRIGHT compared with AC on changes in psychological, emotional, and social well-being in HNC survivors at post-treatment and 1- and 3-months post-intervention relative to baseline 7. To evaluate the feasibility of BRIGHT, delivered via a tablet-based telemedicine, as a strategy to treat BID in HNC survivors 8. To evaluate the acceptability of BRIGHT to as a strategy to treat BID in HNC survivors 9. To determine the association of demographic variables with therapeutic alliance between the study participant and psychologist
Endpoints:	<u>Primary Endpoint:</u> Change in BIS score from baseline to 1-month post-intervention <u>Select Secondary Endpoints:</u> 1. Change in IMAGE-HN score from baseline to 1-month post-intervention. 2. Change in BICSI scores from baseline to 1-week post-intervention 3. Clinical response (BIS score at 1-month post-intervention that is less than the BIS score at baseline) 4. Change in BIS score from baseline to 3-months post-intervention 5. Change in Shame and Stigma Scores from baseline to 1- and 3-months post-intervention 6. Change in PROMIS SF v1.0-Depression 8a scores from baseline to 1-month post-intervention and baseline to 3-months post-intervention 7. Change in PROMIS SF v1.0-Anxiety 8a scores from baseline to 1-month post-intervention and baseline to 3-months post-intervention. 8. Change in PROMIS SF v2.0-Social Isolation 8a scores from baseline to 1-month post-intervention and baseline to 3-months post-intervention 9. Change in PROMIS SF v2.0-Satisfaction with Social Roles and Activities 8a scores from baseline to 1-month post-intervention and baseline to 3-months post-intervention
Study Population:	The study population will consist of head and neck cancer survivors with no evidence of disease, 18 years of age or older, of all races and sexes, with BID following treatment of HNC
Phase or Stage:	N/A

Description of Sites/Facilities Enrolling Participants:	The study will be conducted, and participants enrolled, at a single site, 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:	BRIGHT is 5 sessions of weekly, 60-minute, tablet-based, manualized individual tele-CBT targeting the behavioral and attitudinal components of HNC-related BID.
Study Duration:	24 months
Participant Duration:	4 months

1.2 SCHEMA

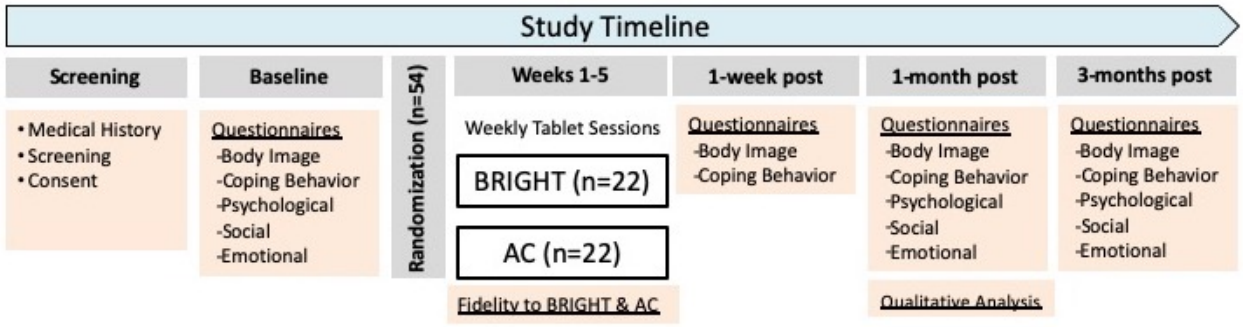


Fig. 1. Study Schema. Following completion of baseline questionnaires, participants will be randomized to 5 weeks of BRIGHT or AC, then complete validated measures of BID, body image coping behavior and psychological, social, and emotional well-being at 1-week, 1-month, and 3-months post-intervention to assess the impact of BRIGHT on changes in BID and the role of body image coping behavior as a mediator of changes in BID.

1.3 SCHEDULE OF ACTIVITIES

Table 1. Schedule of Activities for BRIGHT and Active Control (5 weeks) and follow up (3 months)

	Pre Screen (-60 to 1)	Visit 1 Day 1[a]	Visit 2 Day 8 ±14	Visit 3 Day 15 ±7	Visit 4 Day 22 ±7	Visit 5 Day 29 ±7	Visit 6 Day 36 ±7	Visit 7 Day 43 ±14	Visit 8 Day 64 ±14	Visit 9 Day 124±14	For Details, see section
Informed Consent											
Review Study Eligibility[b]	X										*5*
Informed Consent[c]	X										*10.1.1*
Study Procedures											
Randomization		X									*6.3*
Demographics		X									*8.1*
Clinical and Oncologic History		X									*8.1*
ASI-R		X									*8.1*
Monitoring											
AS/SAE Assessment			X	X	X	X	X	X	X	X	*8.3*
Medication Assessment			X	X	X	X	X	X	X	X	*8.3*
Intervention Administration											
BRIGHT or AC			X	X	X	X	X				*6.1*
Efficacy Evaluation											
Body Image Scale[d]	X							X	X	X	*8.1*
IMAGE-HN[d]		X						X	X	X	*8.1*
PROM Assessments											
BICSI[d]		X						X	X	X	*8.1*
Shame and Stigma Scale[d]		X							X	X	*8.1*
PROMIS SF v1.0-Depression 8a[d]		X							X	X	*8.1*
PROMIS SF v1.0-Anxiety 8a[d]		X							X	X	*8.1*
PROMIS SF v2.0-Social Isolation 8a[d]		X							X	X	*8.1*
PROMIS SF v2.0-Social Roles 8a[d]		X							X	X	*8.1*
EORTC QLQ-HN35[d]		X							X	X	*8.1*
Other Evaluations											

Intervention Fidelity			X	X	X	X	X				*6.2*
Patient Adherence			X	X	X	X	X				*6.4*
Program Evaluation								X			*8.1*
WAI-SR				X			X				*8.1*

[a]: Every effort should be made to minimize the time between randomization and starting treatment
[b]: Eligibility assessed using information in the electronic medical record as well as a screening Body Image Scale
[c]: Written informed consent and HIPAA must be obtained prior to performing and protocol-specific procedures, including baseline evaluations. To optimize participant and researcher safety during the COVID-19 pandemic, informed consent may be obtained in person using a paper informed consent document or electronically using the eConsent.
[d]: Sites are encouraged to administer PROMs using a site-based electronic device. If that is not feasible, administration of PROMs using a paper-based format is also acceptable. Sites are encouraged to align PROM assessments with clinic visits to facilitate in-person collection. In situations in which in-person collection is not feasible, PROMs may be collected via mail or email at the study coordinator's discretion. When possible. PROMs should be completed prior to any other study procedures (following informed consent) and before clinic visits in which clinical information will be discussed to avoid biasing the patient's responses to the questions.

Acronyms: AC, Active Control; AE, Adverse Event; ASI-R, Appearance Schemas Inventory-Revised; BICSI, Body Image Coping Strategies Inventory; BRIGHT, Building a Renewed ImaGe after Head & neck cancer Treatment; IMAGE-HN; **I**nventory to **M**easure and **A**ssess ima**G**e disturbanc**E**-**H**ead & **N**eck; SAE, Serious Adverse Event; WAI-SR, Working Alliance Inventory-Short Revised

2 INTRODUCTION

2.1 STUDY RATIONALE

Head and neck cancer (HNC) arises in cosmetically and functionally critical areas, resulting in substantial life-altering morbidity related to disfigurement, difficulty swallowing, and challenges speaking[1,2]. As a result, 75% of HNC survivors express body image concerns[3,4]. When severe, these concerns result in body image disturbance (BID), a multidimensional construct characterized by a displeasing self-perceived change in appearance and/or function[4-6]. Although BID is a source of significant morbidity and associated with stigmatization, social isolation, and decreased quality of life (QOL)[7,8], effective therapies for BID in HNC survivors are lacking[8]. It is therefore critically important to develop and test novel interventions to minimize psychosocial morbidity and improve QOL in this population[7,8].

We have developed and pilot-tested BRIGHT (Building a Renewed ImaGe after Head & neck cancer Treatment), a novel 5-session, manualized cognitive behavioral therapy (CBT) intervention to treat BID in HNC survivors. BRIGHT targets the behavioral and attitudinal components of BID and can be delivered face to face or using a tablet-based telemedicine format. In our single-arm pilot study of BRIGHT, participants were given the option to select their delivery platform and overwhelmingly enrolled into tablet-based BRIGHT (n=10) instead of face to face BRIGHT (n=1). This pilot study showed that tablet-based BRIGHT (n=10) is feasible (100% of sessions completed), is acceptable to patients (89% highly likely to recommend it), has the potential to decrease BID (mean decrease of 4.56 in BIS scores from baseline to 1-month post intervention (95% CI 1.55, 7.56), and may mediate a reduction in BID by improving body image coping behavior.

In this proposal, we extend our initial research with a pilot randomized controlled trial (RCT) to examine the clinical impact and behavioral mechanistic underpinnings of BRIGHT on BID in HNC survivors. This proposed project will evaluate the preliminary clinical impact and behavioral mechanism of a novel psychobehavioral intervention delivered via a scalable, tablet-based telemedicine platform, thereby advancing our conceptual understanding of BID and establishing new treatment paradigms to directly address the lack of effective treatment for BID in HNC survivor. HNC survivors with BID will be randomized to 5-weeks of tablet-based BRIGHT or tablet-based active control (AC) (patient-centered videos about HNC survivorship care. Participants will complete the Body Image Scale (a validated measure of BID[9]; primary endpoint), the Body Image Coping Strategies Inventory (a validated measure of body image coping behavior[10]; behavioral mediator) and measures of psychological, social, and emotional well-being (secondary endpoints) at baseline, 1-week, and 1-month and 3-month post-intervention.

2.2 BACKGROUND

2.2.1 PYSCHOSOCIAL MORBIDITY IN HEAD AND NECK CANCER SURVIVORS

HNC, which arises in cosmetically and functionally critical areas (tongue, mandible, larynx, and neck) is diagnosed in 65,000 patients in the US annually[11]. HNC results in life-altering morbidity related to disfigurement, difficulty swallowing, impaired smiling, and challenges speaking[12]. Because changes occur in highly visible, socially significant parts of the body that are integral to self-conception, communication, and interpersonal relationships[7,8,13], 75% of HNC survivors express body image concerns[3,4]. When severe, these concerns result in BID, a multidimensional construct characterized by a displeasing self-perceived

change in appearance and/or function[6,7]. Morbidity from BID includes social isolation[14], stigmatization[7], depression[13,15], decreased intimacy[16], and worse QOL[7,8]. Due to this psychosocial morbidity, survivors of HNC are 2-times more likely to die from suicide than survivors of any other cancer[17].

2.2.2 PRIOR INTERVENTIONS TO TREAT BID IN HNC SURVIVORS

Managing BID is a key component of HNC survivorship care[12]. Unfortunately, no effective therapies for BID in HNC survivors have been described[8]. Researchers have evaluated the effect of cosmetic rehabilitation[18] and skin camouflaging[19] on BID in HNC survivors; neither intervention was effective at treating BID. As a result, treatment of BID in HNC survivors represents a significant unmet survivorship need[20]. It is thus critically important to address the lack of treatments for BID in HNC survivors to prevent continued psychosocial morbidity and decreased QOL[8].

2.2.3 TIME-LIMITED CBT FOR THE TREATMENT OF BID IN NON-HNC POPULATION

Stand-alone, time-limited CBT produces durable reductions in the severity of BID in non-disfigured patients with eating or body dysmorphic disorders[21-23], in part by improving body image coping behavior[24]. However, because HNC survivors have highly visible and socially significant impairments and disfigurement, they face a different set of body image concerns than patients with eating or body dysmorphic disorders[5]. No studies have demonstrated the efficacy or mechanism of action of CBT for BID in HNC survivors[8,25].

2.2.4 CONTENT OF BRIGHT

BRIGHT was developed using an intervention mapping approach[26]. Our qualitative work with HNC survivors identified key domains of HNC-related BID which BRIGHT targets: personal dissatisfaction with appearance, other-oriented appearance concerns, appearance concealment, distress with functional impairments, and social avoidance[27].

2.2.5 TELEMEDICINE DELIVERY PLATFORM

Cancer survivors face unique access-to-care barriers for face to face psychosupportive care[28]. For HNC patients, travel burden (due to the regionalization of HNC care[29,30]) is a critical barrier to psychosupportive care and contributes to excess morbidity and mortality[31,32]. HNC survivors also face physical access barriers that prevent face to face CBT including fatigue and treatment toxicity. As a result, innovative approaches to deliver psychobehavioral interventions to HNC survivors are needed[33,34]. Telemedicine is a promising solution because it decreases travel burden[35], increases access to care[36], and provides effective behavioral health interventions[37] (including CBT[28,38]).

We assessed the feasibility of delivering BRIGHT via patient-owned technology. Although a majority of our population owned a video-enabled device (smart phone=83%, tablet=36%, computer=64%, none=6%) and had home internet access (88%), we elected to provide each participant with the same video platform (tablet) and internet connection (cellular-enabled Wi-Fi) to enhance the standardization and rigor of our approach.

Our pilot data suggest that telemedicine is the preferred strategy to deliver CBT interventions to HNC survivors with BID. When patients chose the delivery method of BRIGHT (face to face or tablet-based) in our single-arm trial, tablet-based BRIGHT was overwhelmingly preferred (100% of patients traveling >25 miles (8/8); 67% (2/3) of patients traveling ≤ 25 miles) because of travel considerations, convenience, and flexibility.

2.2.6 FEASIBILITY AND ACCEPTABILITY OF BRIGHT

Feasibility and acceptability of BRIGHT was evaluated in a single-arm clinical trial (NCT03518671). BRIGHT was found to be highly feasible and acceptable to patients in terms of the timing, method of delivery, duration, and content of the intervention (**Table 2**).

Table 2. BRIGHT Feasibility and Acceptability	
Feasibility	
BRIGHT session length (median; IQR), minutes	54; 5
BRIGHT session completion, n (%)	45, 100
Major technical issues during BRIGHT sessions, n (%)	0 (0)
Minor technical issues during BRIGHT sessions, n (%)	5 (11.1)
Tablet returned to study team after BRIGHT, n (%)	10 (100)
Study dropout, n (%)	1 (10)
Acceptability to Patients (Program Evaluation)	Mean (SD)
How well did the timing of the program work for you?	4.44 (0.73)
How well did the method of program delivery work?	4.67 (0.5)
How well did the number of sessions work for you?	4.56 (0.53)
How relevant was the content of each session?	4.56 (0.30)
Session 1	4.11 (1.27)
Session 2	4.44 (0.73)
Session 3	4.56 (0.53)
Session 4	4.89 (0.33)
Session 5	4.78 (0.44)
How likely are you to recommend BRIGHT?	4.89 (0.33)
#Scale 0-5; higher scores indicate greater satisfaction.	

2.2.7 PRELIMINARY CLINICAL IMPACT OF BRIGHT ON BID

BRIGHT demonstrated high levels of clinical activity in this population of HNC survivors with BID in our single-arm pilot trial[39]. Eighty-nine percent of participants (8/9) experienced improvement in their BID at 1-month post-BRIGHT relative to baseline, pre-treatment levels. The clinical effect of BRIGHT on BID was large (**Fig. 2**); BRIGHT was associated with a mean decrease of 4.56 in BIS scores from baseline to 1-month post intervention (95% CI 1.55, 7.56). This clinical effect on BID persisted at 3 months post-BRIGHT relative to baseline (mean of the difference of BIS scores from baseline to 3-months post = 3.56; 95% CI 1.15 to 5.96).

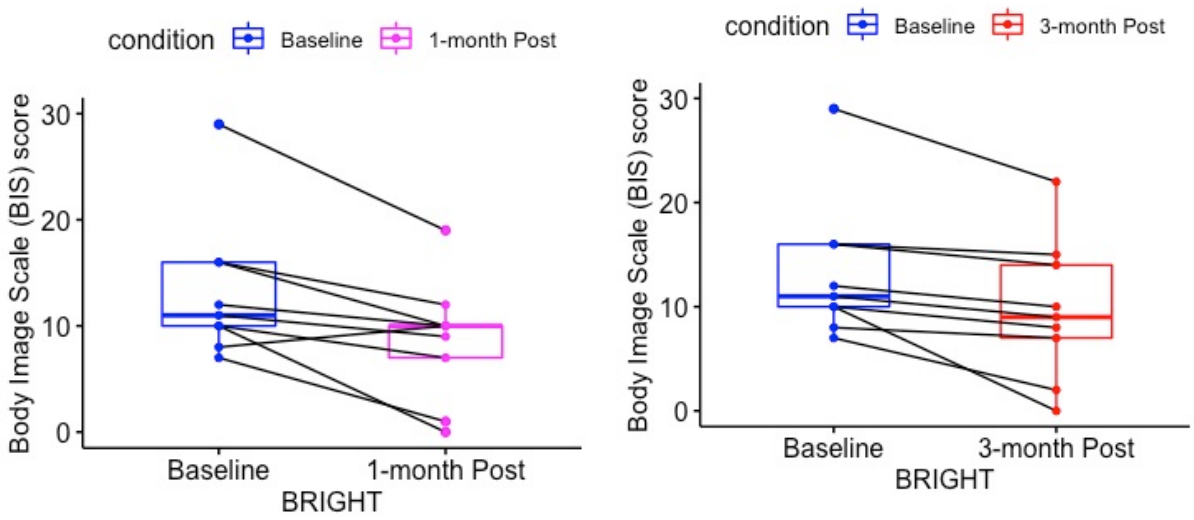


Fig. 2. A) Decrease in the severity of body image disturbance (as determined by Body Image Scale scores) at 1-month post-BRIGHT relative to baseline; **B)** Decrease in the severity of body image disturbance (as determined by Body Image Scale scores) at 3-months post-BRIGHT relative to baseline.

2.2.8 PRELIMINARY CLINICAL IMPACT OF BRIGHT ON HNC-RELATED QUALITY OF LIFE

BRIGHT was associated with improvements in psychosocial aspects of HNC-related QOL in our single-arm pilot trial of BRIGHT[39]. Specifically, BRIGHT was associated with improvements in the trouble with social eating at 1- and 3-months post BRIGHT as measured by the trouble with social eating subdomain of the EORTC QLQHN35 (median trouble with social eating scores = 66.67, 45.83, and 25, at baseline, 1-, and 3-months post-BRIGHT respectively; **Fig. 3**). BRIGHT was also associated with an improvement in the trouble with social contact at 1- and 3-months post BRIGHT as measured by the trouble with social contact subdomain of the EORTC QLQHN35 (median trouble with social contact scores = 40, 26.67, and 16.67 at baseline, 1-, and 3- months post-BRIGHT respectively). BRIGHT was not associated with improvements in depression, anxiety, or shame and stigma post-treatment relative to baseline.

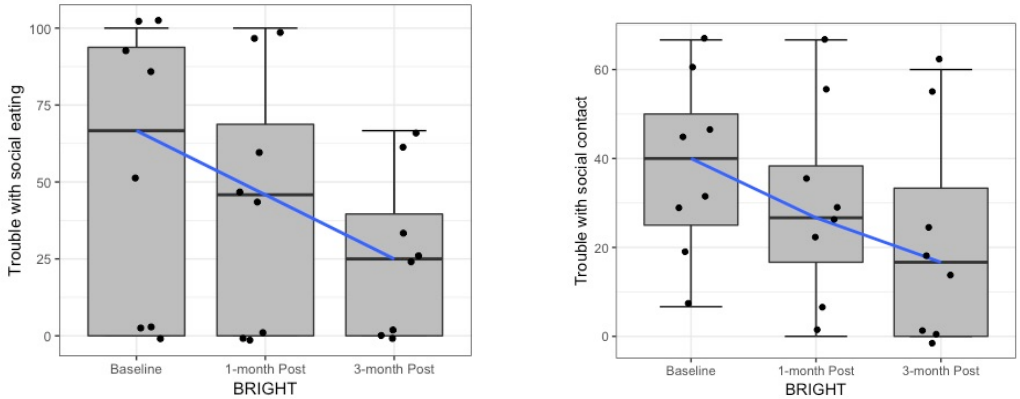


Fig. 3. A) Decrease in difficulty with social eating (as determined by EORTC QLQ-H&N35 Trouble with Social Eating Subscale scores) at 1- and 3-months post-BRIGHT relative to baseline; **B)** Decrease in difficulty with social contact (as determined by EORTC QLQ-H&N35 Trouble with Social Contact Subscale scores) at 1- and 3-months post-BRIGHT relative to baseline

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

Overall, this research study poses no more than minimal risks to participants. The single-arm pilot study of BRIGHT was a minimal risk study that was approved by the MUSC IRB under an expedited review (45CFR46.110). No formal DSMB was required, although a Data and Safety Monitoring Plan (DSMP) with PI and IRB-based oversight was created. The main study procedures include completion of questionnaires, which are generally considered minimal risk. There are no physical, financial, legal, social, or cultural, risks to the study participants by joining this study. The primary risks of the study are 1) psychological/emotional distress and 2) breach of privacy/confidentiality.

Psychological/emotional distress: Subjects may experience adverse psychological reactions such as anxiety, depression, stress, or distress as a result of discussing issues related to cancer, body image, stigmatization, isolation, coping strategies, or social support. These issues may occur during the completion of study questionnaires (baseline or post-treatment) or during the intervention (BRIGHT or AC). However, based on our prior and ongoing research, we expect that low rates of participant distress and believe that this risk is minimal. Nevertheless, we do have a specific protocol should a participant become distressed as a result of participation in this study. The project coordinator and Dr. Maurer, the study psycho-oncologist both have extensive experience dealing with this patient population and appropriate safeguards have been put in place during our pilot work to mitigate against this risk in either situation.

Breach of privacy/confidentiality: 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.

2.3.2 KNOWN POTENTIAL BENEFITS

Based on our pilot data about the clinical impact of BRIGHT on BID, we hypothesize that participants in the BRIGHT arm of the study will have a reduction in the severity of their BID as well as improvement in their psychological, social, and emotional well-being). However, although we hypothesize a direct benefit to participants in the BRIGHT arm (in terms of BID, psychological, social, and emotional well-being), it is unknown whether patients will experience a direct benefit. Data generated from this proposal are expected to provide benefits to society by enhancing our theoretical models of how cognitive-behavioral interventions may help treat BID in cancer survivors. The study is also expected to have broad significance and therapeutic implications beyond BID through development of a novel platform to deliver a variety of psychobehavioral interventions to cancer survivors.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

The decision to participate in this research will be voluntary and individuals may refuse to take part or choose to stop taking part at any time. Participants will also be encouraged to take their time when answering questions and may decline to answer any question at any time. If patients become upset talking

about their cancer and the barriers that they faced, they will be offered a referral to the HCC Behavioral Medicine program (which is covered by most health insurance programs) or the HCC Social Worker who will offer links to other HCC and community resources

Measures to protect against psychological and emotional distress are described below. Participants will be reminded that the decision to initiate and/or continue participating in this research is voluntary. Participants will be informed from the outset that they are free to terminate the assessments, procedures, or therapy sessions at any time and/or refrain from answering any questions that make them uncomfortable. The interviewers are trained researchers who are experienced in the conduct of interviews related to psychosocial aspects of cancer. Our past experience using these study measures suggest that data collection using these instruments can be conducted without undue psychological distress or exacerbation of symptoms among this population (HNC survivors with body image concerns). The study participant will be encouraged to take time when answering questions and may refuse to answer any question at any time during the study.

If at any point during the assessment, treatment, or follow-up period, subjects are in need of medical management, psychiatric consultation, or psychiatric hospitalization, they will be evaluated, and referral or treatment will be provided as indicated. If a subject becomes suicidal, emergency psychiatric assessment will be arranged. The subject will be closely monitored clinically until he/she is no longer suicidal, or an appropriate care plan is in place.

If a participant has a psychological adverse event filling out a questionnaire, the program coordinator will immediately contact Dr. Maurer, a licensed clinical psychologist and the designated study psycho-oncologist, to immediately asses the subject and determine the appropriate course of action. In the event that Dr. Maurer is not available, a fellow licensed psychologist who works in the HCC Behavioral Medicine program will be contacted. Immediate backup and support will be available. In situations in which suicidal ideation (or other psychiatric emergency) is endorsed during completion of study instruments and Dr. Maurer or immediate backup is not available, patients will be referred to the emergency room for immediate psychiatric assessment.

Standard safeguards are also in place in case an adverse psychological reaction occurs during a BRIGHT (or AC) telemedicine session. These include determination of the appropriateness of the participant for home-based telemental health care, determination of the adequacy of infrastructure and technology, site assessments and procedures (obtaining patient's address and local 9-1-1/Emergency medical service provider; local provider contact information, alternate patient and emergency contact information), and monitoring of risk during treatment (symptom levels, self-harm ideation, intention to harm others, changes in setting/patient situation) as described in the DSMP.

All cases of possible psychological distress noted by study personnel will be reported to the PI. In situations in which a participant has psychological distress from participation in the study of which the study team is not aware, participants will be encouraged to notify the PI directly. These adverse events will be reported directly to the IRB per protocol. If project staff believe that a subject is distressed by participation in the study, the PI will be notified and will contact the subject to assess distress and assure subject safety.

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 3. Study Objectives and Endpoints

OBJECTIVES	ENDPOINTS
Primary	
To assess the clinical efficacy of BRIGHT compared with AC on BID in HNC survivors as determined by change in BIS scores at 1-month post-intervention relative to baseline	Change in BIS score from baseline to 1-month post-intervention
Secondary	
To assess the clinical efficacy of BRIGHT compared with AC on BID in HNC survivors as determined by change in IMAGE-HN scores at 1-month post-intervention relative to baseline and 3-months post-intervention relative to baseline	Change in IMAGE HN Scores from baseline to 1-month post-intervention and from baseline to 3-months post-intervention
To explore the behavioral mechanism of action of BRIGHT on changes in BID in HNC survivors as measured by the change in BICSI scores at 1-week post-intervention relative to baseline.	Change in BICSI scores from baseline to 1-week post-intervention

Table 3. Study Objectives and Endpoints	
OBJECTIVES	ENDPOINTS
To provide preliminary estimates of the clinical effect of AC on BID in HNC survivors as determined by change in BIS scores at 1-month post-intervention relative to baseline	Change in BIS score from baseline to 1-month post-intervention
To estimate the activity of BRIGHT compared with AC on BID in HNC survivors in terms of clinical response as measured by improvement in BIS scores at 1-month post-intervention relative to baseline	Clinical response (BIS score at 1-month post-intervention that is less than the BIS score at baseline)
To assess the clinical efficacy of BRIGHT compared with AC on BID in HNC survivors as determined by change in BIS scores at 3-months post-intervention relative to baseline	Change in BIS score from baseline to 3-months post-intervention
To evaluate the preliminary clinical efficacy of BRIGHT compared with AC on changes in psychological, emotional, and social well-being in HNC survivors as determined by change in respective PROM scores at 1- and 3-months post-intervention relative to baseline	Change in Shame and Stigma Scores from baseline to 1- and 3-months post-intervention
	Change in PROMIS SF v1.0-Depression 8a scores from baseline to 1-month post-intervention and baseline to 3-months post-intervention
	Change in PROMIS SF v1.0-Anxiety 8a scores from baseline to 1-month post-intervention and baseline to 3-months post-intervention.
	Change in PROMIS SF v2.0-Social Isolation 8a scores from baseline to 1-month post-intervention and baseline to 3-months post-intervention
	Change in PROMIS SF v2.0-Satisfaction with Social Roles and Activities 8a scores from baseline to 1-month post-intervention and baseline to 3-months post-intervention
	Change in EORTC QLQ-HN35 scores from baseline to 1-month post-intervention and baseline to 3-months post intervention
Feasibility	
To evaluate the feasibility of BRIGHT, delivered via a tablet-based telemedicine, as a strategy to treat BID in HNC survivors	Intervention session duration (minutes)
	Intervention session completion rate
	Number of technical issues with tablet platform
	Return of study-issued tablet
	Study dropout
Acceptability	
To evaluate the acceptability of BRIGHT to as a strategy to treat BID in HNC survivors	Timing of Intervention (0-5 Likert scale)
	Method of Intervention delivery (0-5 Likert scale)
	# of Intervention sessions (0-5 Likert scale)

Table 3. Study Objectives and Endpoints	
OBJECTIVES	ENDPOINTS
	Intervention content relevance (0-5 Likert scale)
	Overall satisfaction with the Intervention (0-5 Likert scale)
	Likelihood of recommending the Intervention (0-5 Likert scale)
To determine the association of demographic variables with therapeutic alliance between the study participant and psychologist	Age, race, sex, Working Alliance Inventory- Short Revised score
Acronyms: AC, Active Control; ASI-R, Appearance Schemas Inventory-Revised; BICSI, Body Image Coping Strategies Inventory; BID, Body Image Disturbance; BIS, Body Image Scale; BRIGHT, Building a Renewed ImaGe after Head & neck cancer Treatment; HNC; Head and Neck Cancer, IMAGE-HN; **I**nventory to **M**easure and **A**ssess ima**G**e disturbanc**E**-**H**ead & **N**eck; WAI-SR, Working Alliance Inventory-Short Revised	

4 STUDY DESIGN

4.1 OVERALL DESIGN

We will conduct a single-site, non-blinded, parallel-group, RCT of BRIGHT versus AC for the management of BID in surgically-managed HNC survivors. The study is designed to test the following hypotheses: 1) BRIGHT will result in a less severe BID relative to AC (primary objective) and 2) Improvements in body image coping behavior from baseline to 1-week post intervention will partially mediate a decrease in BID from baseline to 1-month post intervention.

In this pilot RCT, participants will be allocated to the two study arms (BRIGHT or AC) as follows. Upon enrollment and completion of the baseline assessments, patients will be randomized 1:1 to BRIGHT or AC using a permuted block randomization method, with randomly selected block sizes of 2 or 4. Randomization will occur at the individual patient level. Given the impossibility of delivering BRIGHT in a non-blinded fashion, allocation concealment will be non-blinded. The study statistician 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 intention-to-treat population for the efficacy analysis.

BRIGHT is 5 sessions of weekly, 60-minute, tablet-based, manualized individual tele-CBT targeting the behavioral and attitudinal components of HNC-related BID. BRIGHT focuses on adjustment to disfigurement, teaches coping and problem-solving skills, and addresses the behavioral implications of BID.

In this RCT, BRIGHT will be compared with AC. AC is educational information about HNC survivorship developed (with permission) using resources from the NCI, American Head & Neck Society, Thyroid Head and Neck Cancer Foundation (THANC), and MUSC. AC consists of 5 weekly 30-minute sessions and is delivered one-on-one via a tablet-based telemedicine platform. AC replicates the number of sessions (5), frequency (weekly), and delivery method of BRIGHT (tablet-based telemedicine platform) but differs in content to isolate the 'active' ingredient in BRIGHT. AC was originally matched to BRIGHT for session duration (60 minutes) but was decreased to 30 minutes/session based on feedback during pilot testing from HNC survivors.

4.2 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[40] 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[41]. As a result, the RCT design will provide us with more precise estimates of the effect size and sample size of the BRIGHT intervention relative to AC in preparation for the definitive phase III RCT[42].

An alternative approach is to compare BRIGHT to UC instead of AC. UC for HNC survivors with BID is educational material provided by HNC providers during routine survivorship visits[7]. Comparison to AC is a strength of our approach because AC is matched by duration, frequency, number, and delivery method and delivered using the same tablet platform as BRIGHT. The matching of dose and delivery format between BRIGHT and AC allows us to isolate the role of BRIGHT content in treating BID as opposed to other factors that might confound an association between BRIGHT and improvements in BID were BRIGHT compared with UC (e.g. receipt of the tablet, additional contact with the HNC team).

4.3 JUSTIFICATION FOR INTERVENTION

4.3.1 JUSTIFICATION FOR THE MODE OF DELIVERY

Cancer survivors face unique access-to-care barriers for face to face psychosupportive care[28]. For HNC patients, travel burden (due to the regionalization of HNC care[29,30]) is a critical barrier to psychosupportive care and contributes to excess morbidity and mortality[31,32]. HNC survivors also face physical access barriers that prevent face to face CBT including fatigue and treatment toxicity. As a result, innovative approaches to deliver psychobehavioral interventions to HNC survivors are needed[33,34]. Telemedicine is a promising solution because it decreases travel burden[35], increases access to care[36], and provides effective behavioral health interventions[37] (including CBT[28,38]).

We assessed the feasibility of delivering BRIGHT via patient-owned technology. Although a majority of our population owned a video-enabled device (smart phone=83%, tablet=36%, computer=64%, none=6%) and had home internet access (88%), we elected to provide each participant with the same video platform (tablet) and internet connection (cellular-enabled Wi-Fi) to enhance the standardization and rigor of our approach.

Our pilot data suggest that telemedicine is the preferred strategy to deliver CBT interventions to HNC survivors with BID. When patients chose the delivery method of BRIGHT (face to face or tablet-based) in our single-arm trial, tablet-based BRIGHT was overwhelmingly preferred (100% of patients traveling >25 miles (8/8); 67% (2/3) of patients traveling $\leq$ 25 miles) because of travel considerations, convenience, and flexibility.

4.3.2 JUSTIFICATION FOR THE NUBMBER, FREQUENCY, AND TIMING OF INTERVENTION CONTACTS

A needs assessment conducted within our prospective cohort study of BID in HNC survivors[43] informed the timing (immediately after HNC treatment), setting (one-one psychotherapy), and delivery method (telemedicine or face to face) of BRIGHT. These facets of BRIGHT delivery were subsequently confirmed in our single-arm pilot trial of BRIGHT (**Table 4**)

Table 4. Acceptability of Timing, Frequency, Duration, and Content of BRIGHT from the Single-Arm Pilot Trial (n=9)

Acceptability to Patients	Mean (SD)
How well did the timing of the program work for you?	4.44 (0.73)
How well did the method of program delivery work?	4.67 (0.5)
How well did the number of sessions work for you?	4.56 (0.53)
How relevant was the content of each session?	4.56 (0.30)
Session 1	4.11 (1.27)
Session 2	4.44 (0.73)
Session 3	4.56 (0.53)
Session 4	4.89 (0.33)
Session 5	4.78 (0.44)
How likely are you to recommend BRIGHT?	4.89 (0.33)
[#]Scale 0-5; higher scores indicate greater satisfaction.	

4.4 END-OF-STUDY DEFINITION

A participant is considered to have completed the study if he or she has completed the baseline assessment, and the 1-week, 1-month and 3-month follow-up assessments. The end of the study is defined as completion of the 3-month follow-up assessment shown in the SoA, **Section 1.3**. The end-of-study definition will permit sufficient follow-up to capture the primary endpoint, change in BIS scores at 1-month post-intervention relative to baseline, as well as secondary endpoints assessed at 3-months post-intervention.

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:

1. Age ≥ 18 years at the time of screening
2. History of pathologically confirmed invasive SCC (or histologic variant) of the upper aerodigestive tract (oral cavity, pharynx, larynx, nose/paranasal sinuses), carcinoma of a major or minor salivary gland, or cutaneous malignancy of the face or neck
3. History of curative intent surgery with or without adjuvant therapy, with or without reconstruction

4. American Joint Committee on Cancer (AJCC) 8th Edition pathologic stage grouping I-IV
5. Completion of oncologic treatment within 12 months of study enrollment (but no sooner than 6 weeks post-treatment completion)
6. No planned significant HNC ablative or reconstructive surgery (defined by a postoperative inpatient stay of at least three days) during the study intervention or follow-up period as determined by the HNC oncologic surgeon at the time of study accrual
7. Willingness to be randomized to either BRIGHT or AC
8. BIS score $\geq$ 10

5.2 EXCLUSION CRITERIA

Participants who meet any of the following criteria are not eligible to participate in the study:

1. Inability to speak or write English
2. Pre-existing, ongoing CBT services for other disorders and the participant is not willing to discontinue the prior therapy for the duration of the proposed trial.
3. Initiation or adjustment ($\leq$ 3 months of baseline) of psychotropic medication.
4. Severe psychiatric comorbidity (e.g. suicidal ideation, psychosis)
    - The rationale for excluding these patients is that the study protocol may be therapeutically insufficient.

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

5.5.1 ANTICIPATED SCREENING AND ACCRUAL TARGETS

We propose to enroll 52 patients over 19 months to have 44 analytic subjects complete the study. The planned accrual stratified by gender, race, and ethnicity is shown in **Table 5.** 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) HNC is a rare pediatric malignancy 2) the experiences of children with BID are different from those of adults. There is no maximum age to participate in the study. The investigative team has expertise working with adult HNC survivors across a large age range (19-89 years) in prior research. The Head and Neck Tumor Center, where clinic-based recruitment and enrollment will occur, has appropriate facilities to accommodate individuals

in the included age range. Age will be collected, and data will be disaggregated by age to allow for examination of age as a biological variable during data analysis. The age distribution included in the study (all ages ≥ 18) will allow us to evaluate the impact of age on the feasibility, acceptability, and clinical impact of our study intervention.

The planned distribution of subjects by sex in the clinical trial is 50% female and 50% male. The sex distribution for patients is expected to reflect the demographics of our target population (HNC survivors with BID following surgery at the Medical University of South Carolina [MUSC]) based on our pilot data. There are no specific outreach programs for recruiting based on sex. Subjects will not be excluded from this study based on sex. Sex will be collected, and data will be disaggregated by sex to allow for examination of sex as a biological variable during data analysis.

Patients of all races and ethnicities will be recruited for the study in proportion to their existence in the study population (HNC survivors with BID following surgery at MUSC). The planned distribution of subjects by self-identified race in the trial is 78% white, 19% African American and 3% other. The rationale for the selection of racial proportions in the study is that race is not a known risk factor for BID. The planned distribution of subjects by self-identified ethnicity in the trial is 97% non-Hispanic and 3% Hispanic. The rationale for the selection of ethnic proportions in the study is that ethnicity is not a known risk factor for BID. Race will be collected, and data will be disaggregated by race to allow for examination of race as a biological variable during data analysis.

Table 5. Planned Recruitment by Race, Ethnicity, and Gender

	Ethnic Categories				
Racial Categories	Not Hispanic or Latino		Hispanic or Latino		Total
	Female	Male	Female	Male	
White	17	18	1	1	37
African American	3	3	0	0	6
Asian	1				1
Other					
Total	21	21	1	1	44

5.5.2 ANTICIPATED ACCRUAL RATE AND ACCRUAL FEASIBILITY

The anticipated accrual rate over the course of the study is 52 accrued patients over 19 months to have 44 analytic subjects complete the study. This accrual rate includes a 20% attrition due to study withdrawal or development of a clinical event that makes the patient non-evaluable. These estimates are based on pilot data from our single-arm pilot trial of BRIGHT. There are no specific accrual targets based on patient characteristics (sex, age, racial/ethnic group). For the proposed study, we predict an accrual rate of 2.3 subjects/month. We expect a slightly higher rate of accrual for the proposed trial because we have refined and optimized our recruitment strategies and SOP based on valuable lessons related to logistics, timing, and methods of screening that we learned while recruiting for the single-arm trial of BRIGHT. Although we would expect an even higher rate of accrual (e.g. 2.5 subjects/month) simply based on improvements that we have made while optimizing the SOP for recruitment, our proposed accrual rate is tempered slightly by the more stringent inclusion criteria that we will be using for the proposed trial. Although our single-arm pilot study included patients with a Body Image Scale

score >1, we refined our inclusion criteria for the proposed study to use a Body Image Scale score of ≥ 10 (a clinically relevant threshold), to allow us to target our intervention more precisely and enhance our ability to evaluate mediation. The revised inclusion criterion is expected to impact recruitment minimally; 91% of patients who accrued to BRIGHT in our pilot study would have been eligible with the new criterion. Accrual for the single-arm pilot averaged 2.2 subjects/month. For the proposed study, we predict an accrual rate of 2.3 subjects/month based on the fact that although we improved our accrual strategy based on our pilot work, we will exclude 10% of previously eligible subjects because of more stringent inclusion criteria. Accruing 2.3 subjects/month, we would reach our goal (n=44) in 19 months

5.5.3 PLANNED SCREENING AND RECRUITMENT STRATEGIES

We will screen for potential participants using the electronic medical record (EMR) for the Head and Neck Tumor Center clinical schedule in collaboration with the HNC clinical team. To screen for study eligibility, the research staff will use the EMR to review clinic schedules for new or returning patients with an appointment who are potentially eligible for the study. These appointments will include both in-person clinic visits to the MUSC Head and Neck Tumor Center or a telemedicine visit with a head and neck oncology provider. Clinic rosters will be reviewed at a minimum of once per week, or more frequently if indicated by changes to the clinic schedule. As such, screening will generally be performed within 7 days of enrollment. After a patient who is potentially eligible for the study is identified, the patient will be contacted during the previously identified in-person clinic visit within the MUSC Head and Neck Tumor Center or the telemedicine visit with the head and neck oncology provider to discuss participation in the trial. If it becomes clear that further information is needed to determine study eligibility, the patient will be re-screened pending evaluation of the additional information.

We will recruit participants for the single-site, pilot RCT comparing BRIGHT with AC using a “clinic”-based approach, recognizing that in the era of COVID-19, “clinic” now consists of a combination of in-person and telemedicine visits. In-person recruitment will occur at the Head and Neck Tumor Center of the MUSC NCI-designated Hollings Cancer Center and telemedicine-based recruitment will occur electronically during the telemedicine visit with the head and neck oncology provider that is happening in lieu of the in-person visit. Recruitment for the study will occur using the tested, structured standard operating procedures (SOPs) developed and optimized during our single-arm pilot study of BRIGHT that have been adapted to reflect the addition of telemedicine-based recruitment. This protocol was initially based on structured recruitment protocols from the PI (Evan Graboyes, MD, MPH, FACS) and co-investigator (Katherine Sterba, PhD, MPH) that were previously successfully employed for clinic-based recruitment of HNC survivors into psychobehavioral studies. The original recruitment SOPs have been optimized based on our experiences in the pilot study of BRIGHT to address logistical issues related to coordination of clinic-based screening, enrollment, and distribution of the tablet-based platform for BRIGHT delivery. Our experience recruiting for the single-arm study of BRIGHT also demonstrated that the active clinical practice of the PI and his clinical relationship with all members of the multidisciplinary HNC team is a key factor in maximizing recruitment. The study participants may include patients of the PI’s, but will not be exclusively patients of the PI. Other than the notification of the study by the attending physician for potential trial participants, the research team will not ask other HNC clinicians to be directly involved in recruitment. All of the recruitment will be handled by the study coordinator and study team.

5.5.4 STRATEGIES TO ENHNACE RETENTION

We expect to continue the high rate of retention that we demonstrated in our single-arm pilot study through the following four well-established strategies. First, we maintain active communication with participants during the study including prior to and between visits via each patient's preferred mode of contact (e.g. text message, phone call, e-mail). In addition, our pilot study showed us that having the program coordinator contact participants with a reminder message 1-day prior to a scheduled BRIGHT session helped ensure low rates of missed sessions and high rates of retention. Second, BRIGHT was designed using a patient-centered needs assessment approach to ensure that the timing (immediately after HNC treatment), format (one-one psychotherapy), and delivery method (telemedicine) would ensure design of a feasible and acceptable intervention. While the content of BRIGHT will not be active to the patients in the AC arm, the timing and delivery method are the same in both arms of the trial and will thus likely facilitate retention in the AC as well as the BRIGHT arm. Third, we have accounted for the burden of questionnaires while patients are recovering from treatment to ensure that the expected time survey-related time commitment is reasonable. Collection of questionnaires has been optimized in our pilot study to ensure that it is convenient for participants in terms of timing and method of completion. Fourth, participant retention is maximized through up-front careful screening and a thorough informed consent process to ensure that participants capable of, and interested in, participating in a clinical trial enroll.

5.5.5 RETENTION FEASIBILITY

Our pilot single-arm clinical trial of BRIGHT showed that retention for our study is highly feasible (90%; 9/10 participants). The only participant who dropped out was the first participant enrolled in the study. This participant had multiply recurrent HNC and decided, after the first session of BRIGHT, that she had more significant, concurrent competing demands and thus the BRIGHT program was not applicable to her most pressing concerns. Although challenges with retention for cancer studies due to mortality (overall and disease-specific) and treatment toxicity are potentially problematic, our pilot data have shown that these hypothetical factors not significantly impacted retention feasibility. We have also developed exclusion criteria to minimize potential dropout. These include excluding potential participants with:

1. High likelihood of requiring significant HNC surgery during the study period
2. Pre-existing, ongoing CBT services for other disorders
3. Current suicidal or homicidal ideation

These strategies will ensure that retention is feasible, thus ensuring that given our feasible enrollment targets, the study remains appropriately powered.

5.5.6 PARTICIPANT COMPENSATION

We strive to reinforce participants appropriately for attending visits and completing study procedures. Remuneration also occurs on a schedule that provides significantly more compensation at the end of the study time period. In the proposed study, participants will receive up to $125: $25 for enrolling, $50 for the intervention, and $50 for the follow-up questionnaires. Participants will be compensated by check. This level of compensation is viewed as appropriate for the time of the patient and not unduly coercive.

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

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

6.1.1 STUDY INTERVENTION DESCRIPTION

6.1.1.1 BRIGHT

BRIGHT is 5 sessions of weekly, 60-minute, tablet-based, manualized individual tele-CBT targeting the behavioral, attitudinal, and cognitive components of HNC-related BID. The therapy manual and accompanying patient workbook include agendas for each session, the theoretical and clinical rationale supporting the content, homework, and policies for tardiness, attrition, and homework noncompliance. BRIGHT focuses on adjustment to disfigurement, teaches coping and problem-solving skills, and addresses the behavioral implications of BID. BRIGHT addresses the key conceptual domains of HNC-related BID (**Table 6**)[27]. BRIGHT session topics are shown in **Table 7**.

Table 6. Domains of HNC-Related BID Targeted by BRIGHT[27]

Domains
Personal dissatisfaction with appearance
Other-oriented appearance concerns
Appearance concealment
Distress with functional impairments
Social avoidance

Table 7. BRIGHT Session Topics

Session #	Content
1	Introduction to BRIGHT and setting goals for treatment
2	Cognitive behavioral model for body image disturbance
3	Cognitive restructuring – “talking back” to thoughts
4	Avoidance behaviors, safety behaviors, and social support
5	Identifying personal values and thinking ahead

6.1.1.2 AC

AC is educational information about HNC survivorship developed (with permission) using resources from the NCI, American Head & Neck Society, Thyroid Head and Neck Cancer Foundation (THANC), and MUSC. AC consists of 5 weekly 30-minute sessions and is delivered one-on-one via a tablet-based telemedicine platform. The 5 sessions include of AC are shown in **Table 8**. AC was pilot tested with HNC survivors and refined based on their feedback to ensure its feasibility, appropriateness, and relevance.

Table 8. AC Session Topics

Session #	Content
1	HNC survivorship
2	HNC physical late and long-term treatment toxicity
3	HNC psychosocial late and long-term treatment toxicity
4	Health maintenance
5	Financial toxicity and return-to-work after HNC

6.1.2 ADMINISTRATION AND/OR DOSING

Both BRIGHT and AC will be delivered using the same tablet-based telemedicine delivery platform. Upon enrollment, subjects in each arm receive, and are trained to use, a study-issued, Wi-Fi and 4GLTE cellular-enabled iPads (32 Gb, 9.7-inch screen with LED retina display, 1.2 MP front-facing camera with 780 p video-resolution). Each iPad is locked to prevent downloading of additional applications and pre-loaded with a SIM Card to enable cellular communication. Cellular service is provided by Verizon (99.86% coverage of South Carolina). The iPad is preloaded with Vidyo, a HIPAA-compliant, video teleconference platform. Vidyo allows face to face communication, but also includes a within-video text feature for aphonic (due to surgical removal of their larynx) or severely dysarthric (due to surgical removal of their tongue) HNC patients. Subjects receive a hands-on tutorial about how to use Vidyo upon enrollment and a supplemental pictorial instructional booklet for reference at home. To log into a session, the subject clicks on the Vidyo application to enter the pre-assigned teleconference room and connect to the study psychologist (BRIGHT) or electronic information (AC). No user names, logins, or URLs are necessary. At the conclusion of the 5-week intervention, subjects return the iPads to the study team in pre-addressed, stamped, padded mailers.

6.1.2.1 BRIGHT

BRIGHT will be delivered in one-on-one, face-to-face sessions between the study psychologist and participant using a tablet-based telemedicine platform. The BRIGHT intervention consists of five sessions of weekly, 60-minute, tablet-based, manualized individual tele-CBT (see **Section 1.3, Schedule of Activities**). BRIGHT will be delivered by two licensed clinical psychologists at the MUSC Hollings Cancer Center (Stacey Maurer, PhD and Wendy Balliet, PhD). The use of two psychologists to deliver BRIGHT will enhance rigor and external validity and minimize confounding between the experimental intervention and interventionist. Based upon our pilot work, a full-dose of the intervention consists of five sessions within a six-week span with a mean session-length of 45 minutes. The relevant parameters when considering the delivery of BRIGHT include the number, frequency, and duration of tablet-based sessions. 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. Such encounters may also occur in the virtual and social network space through patient support forums and online communities of HNC survivors.

6.1.2.2 AC

AC consists of 5 weekly 30-minute sessions and is delivered one-on-one via a tablet-based telemedicine platform. AC replicates the number of sessions (5), frequency (weekly), and delivery method of BRIGHT (tablet-based telemedicine platform) but differs in content to isolate the 'active' ingredient in BRIGHT (see **Section 1.3, Schedule of Activities**). The relevant parameters when considering the delivery of AC include the number, frequency, and duration of tablet-based sessions to ensure that it is appropriately matched to BRIGHT. The AC matches (and replicates) the duration and frequency of BRIGHT. AC was originally matched to BRIGHT for session duration (60 minutes) but was decreased to 30 minutes/session based on feedback during pilot testing from HNC survivors. Session topics include: 1) HNC survivorship overview; 2) physical long-term HNC treatment toxicity; 3) psychosocial long-term HNC treatment toxicity, 4) health maintenance, and 5) financial toxicity and return-to-work. AC was pilot tested with HNC survivors and refined based on their feedback to ensure its feasibility, appropriateness, and relevance. The videos are stored on the tablet and thus do not require a person for delivery; however, the study coordinator will

initiate and close the telemedicine session as described in the AC SOP, thereby enhancing participant adherence to AC. A full dose of AC is not known. 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. Such encounters may also occur in the virtual and social network space through patient support forums and online communities of HNC survivors.

6.2 FIDELITY

6.2.1 INTERVENTIONIST TRAINING AND TRACKING

6.2.1.1 BRIGHT

Standardization of intervention administration is critical to ensure scientific rigor, validity, reproducibility, and achievement of study objectives. The specific duties necessary to ensure consistent and optimal administration of BRIGHT are detailed in the BRIGHT manual and AC standard operating procedures (SOP). All sessions of BRIGHT and AC will be audio-recorded and randomly selected sessions (20%) will be reviewed by a co-investigator to ensure fidelity of BRIGHT and AC in a manner that is consistent with SOP. If insufficient adherence to the manual is identified, appropriate remediation will occur. For BRIGHT and AC, the study coordinator will keep a tracking log capturing session duration, content delivered, and technical problems with the tablet-based delivery system. Because Dr. Maurer, the study psychologist helped develop BRIGHT, delivered BRIGHT in our single-arm pilot trial, and has experience managing pyscho-oncologic concerns in HNC patients, no additional specific training is planned prior to the delivery of BRIGHT for this trial.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

Bias will be minimized through the randomized permuted block design. Randomization will occur at the individual patient level. Patients will be randomized 1:1 to BRIGHT or AC using a permuted block randomization method, with randomly selected block sizes of 2 or 4. Given the impossibility of delivering BRIGHT 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 using the REDCap randomization module. Randomization errors will be handled as per the modified intention-to-treat population for the efficacy analysis.

6.4 STUDY INTERVENTION ADHERENCE

6.4.1 BRIGHT

Adherence of subjects to BRIGHT study procedures are key to ensure scientific rigor, validity, reproducibility, and achievement of study objectives. Adherence will be assessed with the following

measures: 1) attendance at intervention visits; 2) duration of study visits; 3) homework completion, 4) psychologist rating of patient engagement and material comprehension. Attendance at all study visits are mandatory to remain an active participant. Adherence information will be ascertained from the BRIGHT visit note authored by the study psychologist in a patient-adherence tracking log in the EMR after each study visit and documented in the eCase Report Form (eCRF) after each study visit by the study coordinator.

6.4.2 AC

Adherence of subjects to AC study procedures are key to ensure matching of the delivery format, frequency, duration, and schedule of the control, and thus scientific rigor, validity, reproducibility, and achievement of study objectives. Adherence to AC will be assessed with the following measures: 1) attendance at intervention visits; 2) duration of study visits; and 3) homework completion. Attendance at all study visits are mandatory to remain an active participant. Adherence information will be ascertained by the study coordinator after each study visit and documented in the eCRF.

6.5 CONCOMITANT THERAPY

For this protocol, participants may use antidepressants and anxiolytics at the discretion of their treating providers. Medication usage will be assessed at each study visit and documented in the eCRF.

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.

When a subject discontinues from BRIGHT or AC but not from the study, remaining study procedures will be completed as indicated by the study protocol. If a clinically significant finding is identified (including, but not limited to changes from baseline) after enrollment, the investigator or qualified designee will determine if any change in participant management is needed. Any new clinically relevant finding will be reported as an adverse event (AE).

The data to be collected at the time of study intervention discontinuation will include the following:

- The reason(s) for discontinuing the participant from the intervention, and methods for determining the need to discontinue
- If the participant is due to complete assessments within 2 weeks of being discontinued from the study intervention, those assessments will be administered at the time of discontinuation; if the next scheduled assessments are more than 2 weeks from the discontinuation date, the discontinued

participant will wait for the next scheduled assessment. Thereafter, the participant will be included in all future scheduled assessments, even though not participating in the intervention.

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.

An investigator or the IRB 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
    - Subjects who are enrolled into the study and undergo a significant HNC ablative or reconstructive surgery (defined by a postoperative inpatient stay of at least three days) during the study intervention or follow-up period
    - Subjects who are enrolled in the study and develop a recurrence of their index HNC (local, regional or distant recurrence, radiologic or biopsy-proven) or metachronous second primary cancer (radiologic or biopsy-proven) during the study intervention or follow-up period

The rationale for having these patients discontinue the study is that a significant HN-related surgery, development of a HNC recurrence, or development of a second primary cancer may introduce new body image concerns, confounding the association between BRIGHT (or AC) and changes in BID.

The reason for participant discontinuation or withdrawal from the study will be recorded on the CRF. Subjects who sign the informed consent form and are randomized, regardless of whether or not they received the intervention, will not 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 ASSESSMENTS

To screen for study eligibility, the research staff will use the EMR to review clinic schedules for new or returning patients with a physical appointment in the MUSC Head and Neck Tumor Center or telemedicine visit with a head and neck oncology provider who are potentially eligible for the study. Clinic rosters will be reviewed at a minimum of once per week, or more frequently if indicated by changes to the clinic schedule. As such, screening will generally be performed within 7 days of enrollment. After a patient who is potentially eligible for the study is identified, the patient will be contacted at the previously identified clinic visit (either physically within the MUSC Head and Neck Tumor Center or during the telemedicine visit) to discuss participation in the study as described below. The study coordinator who is screening the clinic schedule weekly will determine whether or not the potential trial participant has consented in EPIC to participate in research studies. For patients who have consented in EPIC to participate in research studies, the study coordinator will recruit using existing protocols for face-face clinic-based recruitment and study-specific documents to describe the study. For patients who have not consented in EPIC to participate in research studies, the head and neck oncology provider for the patient will notify the patient of the study and introduce the study to the potential participant. Following this introduction, if the potential participant is interested in learning additional information about the trial, the study coordinator will recruit using existing standard operating procedures for clinic-based or telemedicine-based recruitment. Patients who meet demographic and oncologic inclusion criteria will complete a screening BIS questionnaire; those with scores $\geq$ 10 will be eligible for the study. Those with scores < 10 will not be eligible for the study, their BIS questionnaire will be shredded, and no personal information about the patient will be saved.

Primary Endpoint

Change in BIS scores. The BIS is a validated, 10-item patient-reported outcome measure (PROM) that assesses the affective, cognitive, and emotional aspects of body image due to cancer or its treatment over the prior 7 days[9]. Responses include 'not at all', 'a little', 'quite a bit', and 'very much', and are scored from 0-3, respectively. Total BIS scores can range from 0-30, with higher scores indicating greater body image dissatisfaction. The BIS is a reliable PROM validated in oncology patients and has been widely used to study BID in patients with HNC[44].

Secondary Endpoints

Behavioral Mediator

Change in Body Image Coping Strategies Inventory (BICSI) scores. The BICSI is a 29-item validated measure of the cognitive and behavioral responses to manage threats to body image[10]. BICSI contains three sub-domains; 1) appearance fixing (altering appearance by covering, camouflaging, or correcting the perceived defect), 2) avoidance (an attempt to escape or avert stressful body-image situations), and 3) positive rational acceptance (acceptance of the challenging event and positive self-care or rational self-talk about one's appearance). Items are scored on a 4-point Likert scale from 'definitely not like me' to 'definitely like me' (0-3). The scores for each subscale are calculated by summing the values for the individual questions and thus range as follows: 1) appearance fixing (0-30), 2) avoidance (0-24), 3) positive rational acceptance (0-33). For each subscale, higher scores indicate greater quantities of each conceptual domain (appearance fixing, avoidance, and positive rational acceptance). Avoidance and appearance fixing are maladaptive means of coping that are associated with dysfunctional schemas, elevated levels of BID and

distress, and poorer psychosocial functioning. Positive rational acceptance is a positive means of coping that is associated with lower levels of BID and distress.

Clinical Activity

Change in IMAGE-HN scores: The IMAGE-HN is a psychometrically sound, 24-item, multi-domain PROM consisting of 4 sub-scales and a global scale that can be used to measure key aspects of HNC-related BID due to HNC or its treatment[45]. Responses include 'Never', 'Rarely', 'Sometimes', 'Often', 'Always', corresponding to a Likert scale of 0-4, respectively. Total IMAGE-HN scores on the global domain (21 questions) range from 0-84, with higher scores indicated greater HNC-related body image dissatisfaction. Raw scores for each sub-scale as well as the global scale can be converted to scaled scores for each, which range from 0-100 with higher scores representing greater HNC-related BID.

Response. Response is defined as a BIS score at 1-month post-intervention that is lower than the BIS score at baseline.

Secondary Measures of Psychosocial Wellbeing

Change in Shame and Stigma Scale scores. The Shame and Stigma Scale is a 20-item, validated, unidimensional PROM that measures four domains (shame with appearance, stigma, regret, and social/speech concerns) in patients with HNC over the prior 7 days[46]. Responses include 'never', 'seldom', 'sometimes', 'often', and 'all the time' and are scored 0-4, respectively. The total score is calculated by summing the individual responses (except for 4 questions which are reverse scored) and thus ranges from 0-80. Higher scores reflect greater shame and stigma from HNC.

Change in PROMIS SF v1.0-Depression 8a scores. PROMIS SF v1.0-Depression 8a is a validated, 8-item measure developed by the NIH to assess self-reported negative mood, views of self, and decreased positive affect and engagement[47]. Items are scored using a 5-point Likert scale from 'never' to 'always' (1-5). The total score is calculated by summing the individual responses and thus ranges from 8-40. Higher scores reflect more severe depressive symptoms.

Change in PROMIS SF v1.0-Anxiety 8a scores. The PROMIS SF v1.0-Anxiety 8a is a validated, 8-item measure developed by the NIH to assess self-reported fear, worry, and hyperarousal[47]. Items are scored using a 5-point Likert scale from 'never' to 'always' (1-5). The total score is calculated by summing the individual responses and thus ranges from 8-40. Higher scores reflect more severe anxiety.

Change in PROMIS SF v2.0-Satisfaction with Social Roles and Activities 8a scores. PROMIS SF v2.0-Satisfaction with Social Roles and Activities 8a is a validated, 8-item, measure developed by the NIH to assess self-reported satisfaction with performing one's usual social roles and activities[48]. Items are scored using a 5-point Likert scale from 'not at all' to 'very much' (1-5). The total score is calculated by summing the individual responses and thus ranges from 8-40. Higher scores reflect more severe anxiety.

Change in PROMIS SF v2.0-Social Isolation 8a scores. PROMIS SF v2.0-Social Isolation 8a is a validated, 8-item, measure developed by the NIH to assess self-reported perceptions of being avoided, excluded or unknown by others[48]. Items are scored using a 5-point Likert scale from 'never' to 'always' (1-5). The total score is calculated by summing the individual responses and thus ranges from 8-40. Higher scores reflect more severe social isolation.

Feasibility

Intervention session duration is defined as the duration (in minutes) for each participant

Intervention session completion is the number of intervention sessions completed by each participant

Technical issues during tablet-based telemedicine sessions. Technical issues include inability to connect to the internet, video conference session, lack of video, lack of audio, insufficient tablet battery power, or any other technology related issues that prevents the session from otherwise functioning in a smooth and timely fashion.

Tablet return is defined as the receipt of the study-issued tablet by the study team within three months of the completion of the five sessions of the intervention.

Study dropout is defined as a participant voluntarily withdrawing from the study for whatever reason

Acceptability
Timing of Intervention will be assessed using a study-specific Likert scale measuring satisfaction with the timing of the intervention relative to the completion of treatment. Scores range from 0-5 with higher scores representing greater satisfaction with the timing of the intervention.

Method of Delivery of the Intervention will be assessed using a study-specific Likert scale measuring satisfaction with the method of delivery of the intervention. Scores range from 0-5 with higher scores representing greater satisfaction with the method of delivering the intervention.

Number of Intervention Sessions will be assessed using a study-specific Likert scale measuring satisfaction with the number of sessions of the intervention. Scores range from 0-5 with higher scores representing greater satisfaction with the number of intervention sessions.

Session content relevance will be assessed using a study-specific Likert scale measuring satisfaction with the content relevance of each session. Scores range from 0-5 with higher scores representing greater satisfaction with the content of the intervention.

Overall satisfaction will be assessed using a study-specific Likert scale measuring overall satisfaction with the intervention. Scores range from 0-5 with higher scores representing greater satisfaction with the intervention.

Likelihood of Recommending the Intervention will be assessed using a study-specific Likert scale measuring likelihood of recommending the intervention. Scores range from 1-5 with higher scores representing greater likelihood of recommending the intervention.

Working Alliance Inventory-Short Revised (WAI-SR) score. The WAI-SR is 12-item measure of working alliance consisting of three subscales assessing: 1) how closely client and therapist agree on and are mutually engaged in the goals of treatment (goals), 2) how closely client and therapist agree on the therapeutic tasks necessary to reach the treatment goals (tasks), and 3) the degree of mutual trust, acceptance, and confidence between client and therapist (bond). Patients score on a 5-point Likert scale ranging from rarely to always (1-5). Subscales scores for each of the subscales (goals, tasks, bond) range from 4-20. Total scores range from 12 to 60 with higher scores representing a stronger working alliance between the therapist and participant.

Covariates

Appearance Schemas Inventory-Revised (ASI-R) Score. The ASI-R is a psychometrically sound, 20-item measure of image investment[49]. The ASI-R consists of two subdomains: Self-Evaluative Salience (of Appearance) and Motivational Salience (of Appearance). Items are scored using a 5-point Likert scale from 'strongly disagree' 'strongly agree' (1-5). Items 1, 4, 5, 9, 11, 12 are reverse scored. The composite ASI-R score is calculated as the mean of the 20 items, and thus composite ASI-R scores range from 1-5. The score for each subscale is also calculated as the mean of its included items. Higher scores reflect greater levels of image investment.

The individual's medical chart will be used to collect information performed as part of an individual's regular medical care are going to be used as a part of collection of trial data. As such, Health Insurance Portability and Accountability Act (HIPAA) rules, other relevant federal or state laws, and local institutional requirements will be followed, as applicable. The following information is to be obtained through review of existing data:

Demographics**.** Demographic characteristics include age, race, ethnicity, sex, marital status, living situation, insurance.

Clinical and Oncologic Characteristics. Clinical characteristics will include body mass index (BMI), comorbid medical conditions, and cancer history. Oncologic characteristics will include HNC tumor subsite, HNC tumor histology, American Joint Committee on Cancer TNM Class and overall stage grouping, type of ablative surgical, type of reconstruction, adjuvant radiation dose, adjuvant chemotherapy dose and agent, and time since completion of treatment.

8.2 SAFETY ASSESSMENTS

N/A

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.3.1 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.

8.3.2 DEFINITION OF SERIOUS ADVERSE EVENTS

A serious adverse event (SAE) will be defined as 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, is medically significant and which the investigator regards as serious based on appropriate medical judgment that is directly due to a study intervention. 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.

8.3.3 CLASSIFICATION OF AN ADVERSE EVENT

8.3.3.1 SEVERITY OF EVENT

- **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".

8.3.3.2 RELATIONSHIP TO STUDY INTERVENTION/EXPERIMENTAL MANIPULATION

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.

8.3.4 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.

8.3.5 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

8.3.6 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.

8.3.7 REPORTING EVENTS TO PARTICIPANTS

N/A

8.3.8 EVENTS OF SPECIAL INTEREST

N/A

8.3.9 REPORTING OF PREGNANCY

N/A

8.4 UNANTICIPATED PROBLEMS

8.4.1 DEFINITION OF UNANTICIPATED PROBLEMS

This protocol uses the definition of Unanticipated Problems (Ups) 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.

8.4.2 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

8.4.3 REPORTING UNANTICIPATED PROBLEMS TO PARTICIPANTS

N/A

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

- Primary Endpoint:

We hypothesize that, compared with patients who receive the AC, patients who receive BRIGHT will have reduced BID as measured by change in BIS scores at 1-month post-intervention relative to baseline. Alternatively, our null hypothesis is that there will be no difference between BRIGHT and AC in terms of improving BID, as measured by change in BIS scores at 1-month post-intervention relative to baseline.

- Secondary Endpoint(s):

We hypothesize that improvements in body image coping behavior (improvement in BICSI scores from baseline to 1-week post intervention) will partially mediate a decrease in BID (reduction in BIS scores from baseline to 1-month post intervention) and this relationship will be maintained at 3-months.

We hypothesize that BRIGHT will improve psychological (larger decrease in Shame and Stigma scores), emotional (larger decrease in PROMIS depression and anxiety scores), and social well-being (larger decrease in PROMIS social roles and social isolation scores) relative to AC at 1- and 3-months post-intervention.

9.2 SAMPLE SIZE DETERMINATION

Our primary objective is to compare change in BIS scores from baseline to 1-month intervention between the BRIGHT and AC arms. The primary endpoint is Δ in Body Image Scale scores from baseline to 1-month post-intervention. We hypothesize that, compared with patients who receive the AC, patients who receive BRIGHT will have reduced BID as measured by change in BIS scores at 1-month post-intervention relative to baseline. Alternatively, our null hypothesis is that there will be no difference between BRIGHT and AC in terms of improving BID, as measured by change in BIS scores at 1-month post-intervention relative to baseline. All power and sample size calculations were performed using PASS 2008 version 08.0.13. Based on data from our prospective cohort study[50] and single-arm pilot of BRIGHT, we estimate the mean Δ in Body Image Scale scores ± SD from baseline to 1-month post are 0.2 ± 5.9 and 4.6 ± 3.9 for control and BRIGHT, respectively. This effect size is clinically significant and realistic given results of other psychobehavioral interventions in breast cancer patients with BID[51,52]. For n=22/arm (proposed sample size), power exceeds 80% for mean difference in change in Body Image Scale scores of at least 3.1 (with SD as large as 4) or mean difference of at least 5.5 (with SD as large as 7) based on two-sided t-test with α=0.1 **(Fig. 4A).** Group sample size of n=22 (AC, BRIGHT) achieved 80.2% power to detect the standardized effect (mean difference in Δ Body Image Scale score from baseline to 1-month divided by the pooled SD=5.62) of 0.78 based on the two-sample *t*-test with two-sided α=0.1 (**Fig 4B**). We will have greater than 90% power for a standardized effect size of 0.93 and greater than 80% power for a standardized effect size of 0.78. These are both considered moderate effect sizes and are feasible for continuous outcomes in the context of variables that are expected to be modulated by the cancer experience. Our power estimate is conservative given our proposed analysis plan using LME regression, which borrows strength over time and is generally more efficient than a *t*-test. As such we anticipate that smaller effect sizes than described above will be detectable. Our selection of relaxed significance (α = 0.1) with maintained power (1 – β = 0.8) is based on the desire to emphasize power over type I error at this

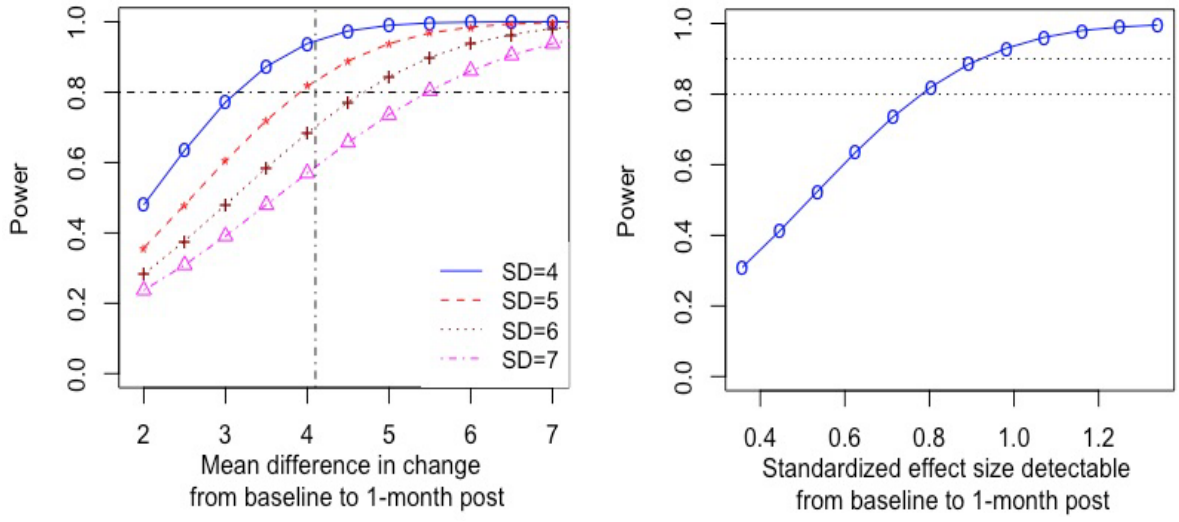


Fig. 4. Power Calculations for (A) Mean difference in Δ in Body Image Scale scores between baseline and 1-month post intervention, comparing BRIGHT and AC; **(B)** standardized effect, comparing Δ in Body Image Scale scores between BRIGHT and AC from baseline to 1-month post intervention

early stage of development (single-site pilot RCT) to ensure follow-up on promising interventions to guide and power a subsequent larger RCT to fully evaluate the efficacy of BRIGHT as a treatment of BID in HNC survivors (i.e. test BRIGHT with significance level of 0.05). We therefore consider our RCT to be appropriately and rigorously designed to detect a clinically meaningful reduction in BID.

In order to have 44 patients eligible for the efficacy analysis in the modified ITT population (see **Section 9.3, Population for Analyses**), we plan to enroll 52 patients. Our sample size is inflated by 20% based on interim accrual data. This inflation account for study dropout and the predictable subset of patients would be enrolled in the study, be randomized to BRIGHT or AC, receive a portion or all of the intervention and then subsequently are withdrawn from the study and non-evaluable due to a major HNC surgery or recurrent or second primary cancer.

Every effort will be made to minimize missing data and lost-to-follow-up participants. Participants will complete assessments at baseline, 1-week post-intervention, 1-month post-intervention, and 3-months 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 our single arm pilot study. In the event that missing data do occur, we will address them via standard multiple imputation procedures[53,54]. As participants will be randomized to treatment, it is unlikely that missing data will produce biased estimates of treatment effect, as observed and unobserved covariates should theoretically be balanced across treatment groups. In general, less than 10% missing data has little impact on study power and does not induce bias regardless of the missing data mechanism[55]. If missing data is greater than 10%, it will be imputed using propensity score[54,56] or Markov Chain Monte Carlo (MCMC) methods[57]. When covariate information is associated with whether the imputed variable values are missing, we will use the propensity score method, which calculates the propensity score from modeling the distribution of the missing indicator variable based on the observed data and then applies an approximate Bayesian bootstrap imputation to each group identified by the propensity score. Otherwise, we will use the MCMC method. The data augmentation will be applied to Bayesian inference with missing data by repeating imputation step (i.e., simulating the missing values based on the observation) and step for exploring the posterior distribution based on the complete sample estimates obtained from the imputation step.

9.3 POPULATIONS FOR ANALYSES

Participants will be defined as evaluable for the primary endpoint (change in BIS from baseline to 1-month post-treatment) and thus included in the efficacy analytic population if they are enrolled in the study and randomized. However, there are two subsets of patients (**7.2, Participant Discontinuation/Withdrawal**) for whom the investigator may discontinue participation due to an 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. Specifically,

1. Subjects who are enrolled into the study and undergo a significant HNC ablative or reconstructive surgery (defined by a postoperative inpatient stay of at least three days) during the study intervention or follow-up period.
2. Subjects who are enrolled in the study and develop a recurrence of their index HNC (local, regional or distant recurrence, radiologic or biopsy-proven) or metachronous second primary cancer (radiologic or biopsy-proven) during the study intervention or follow-up period.

We will also perform an efficacy analysis on the per-protocol analytic dataset, a subset of the ITT population who completed all 5 intervention (BRIGHT and AC) 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 BRIGHT according to the underlying scientific model.

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

Graphical displays such as scatterplots and boxplots will be constructed to demonstrate patterns of individual continuous measures and differences between baseline, 1-week, 1- and 3-months post intervention. Summary descriptive statistics (e.g. frequencies and percent for categorical variables, and mean, median, standard deviation, and range for continuous variables) will be reported. 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(S)

Longitudinally measured BIS scores will be modeled using linear mixed effects (LME) regression with the measures at each time point relative to baseline (denoted by Δ) as the response variable and fixed effects for experimental conditions (BRIGHT, AC), time (1-week, 1-month, and 3-months post intervention) and their interaction. Models will include subject-specific random effects to account for correlation among measures obtained from the same subject over time. We will use qq-plots and histograms to investigate the assumption of approximate normality and consider transformations (e.g., log) as needed. We will assess the functional form of time to account for any non-linear temporal trends and consider transformations as needed. Comparisons of the change from baseline to each time point between conditions will be performed using model-based linear contrasts. Data will be disaggregated by age, sex, and race to allow for analysis of each as biological variables.

9.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

For secondary endpoints related to psychological, emotional, and social well-being, graphical displays such as scatterplots and boxplots will be constructed to demonstrate patterns of individual continuous measures and differences between baseline, 1-week, 1- and 3-months post intervention. Summary descriptive statistics (statistics (e.g. frequencies and percent for categorical variables, and mean, median, standard deviation, and range for continuous variables) will be reported. Longitudinal measures of psychological, social, and emotional well-being will be modeled using LME regression with the measures at each time point relative to baseline (denoted by Δ) as the response variable and fixed effects for experimental conditions (BRIGHT, AC), time (1-week, 1-month, and 3-months post intervention) and their interaction. Models will include subject-specific random effects to account for correlation among measures obtained from the same subject over time. We will use qq-plots and histograms to investigate the assumption of approximate normality and consider transformations (e.g., log) as needed. We will assess the functional form of time to account for any non-linear temporal trends and consider transformations as needed. Comparisons of the change from baseline to each time point between

conditions will be performed using model-based linear contrasts. Data will be disaggregated by age, sex, and race to allow for analysis of each as biological variables.

To evaluate whether the effect of BRIGHT on change in BID at 1-month post-intervention is partially mediated by changes in body image coping behavior at 1-week post intervention, we will perform exploratory mediation analysis. The total effect of the intervention (path *c*) will be partitioned into direct (path *c'*) and indirect effects, which we will test for statistical significance (**Fig. 5**). We will examine the direct effect of the intervention on change in BID (Δ in Body Image Scale score) the mediating effect of change in body image coping behavior (Δ in Body Image Coping Strategies Inventory score) on change in BID, and the effect of the intervention on the mediator (Δ in Body Image Coping Strategies Inventory score). If paths *a, b,* and *c* are statistically significant and *c'* (the direct effect) is reduced compared with *c* (the total effect), then partial mediation criteria are satisfied. The significance of the mediating effect will be tested using robust bootstrapping. Bootstrapping is considered superior to other methods of analyzing indirect effects because bootstrapping provides confidence intervals based on the bootstrap distribution instead of simply p values. In situations with smaller samples and non-normal distributions, the bootstrapping method is more likely to achieve an unbiased estimate of the indirect effect than other methods. The confidence interval for the mediating effect will be provided from the bootstrap analysis with the 'robmed' R package. This analysis will be repeated for change in BID at 3-months post and change in image coping behavior at 1-month post-intervention. Plots of mediated effect will be made to investigate the distribution of data and improve understanding of the relations among the variables. LME regression will be considered to assess the three-way interaction (moderator-intervention-time) for age, sex and race.

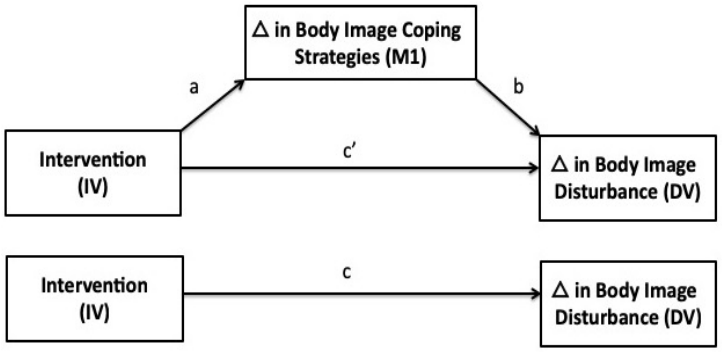


Fig. 5. Exploratory mediator analysis. Changes in body image coping behavior (Mediator [M1]) are hypothesized to mediate the effect of the intervention (independent variable [IV]) on changes in body image disturbance (dependent variable [DV]).

For secondary endpoints related to the feasibility and acceptability objectives, simple frequencies will characterize participant satisfaction with the following aspects of the intervention: timing, method of delivery, number of sessions, content relevance, homework utility, attentiveness of the study psychologist, overall satisfaction, and likelihood to recommend BRIGHT. Descriptive statistics will be presented. Our interdisciplinary team will meet after completion of study data analyses to interpret the implications of these findings for how to refine BRIGHT based on these data in preparation for our future large-scale trial.

9.4.4 SAFETY ANALYSES

N/A

9.4.5 BASELINE DESCRIPTIVE STATISTICS

Baseline characteristics (e.g., demographics, oncologic details, behavioral characteristics) for the BRIGHT and AC arms will be compared and descriptive statistics calculated. Baseline differences between the two groups will be compared using t-tests and chi-square tests, or Wilcoxon rank sum and Fisher's exact tests as appropriate.

9.4.6 PLANNED INTERIM ANALYSES

N/A

9.4.7 SUB-GROUP ANALYSES

Planned sub-group analyses of the primary endpoint will occur based on age, race, and sex to evaluate the impact of inclusion across the lifespan, race, and sex as biologic variables.

9.4.8 TABULATION OF INDIVIDUAL PARTICIPANT DATA

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

9.4.9 EXPLORATORY ANALYSES

N/A

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

10.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Consent forms describing in detail the study intervention, study procedures, and risks will be provided to the participant (either on paper or electronically as an eConsent) and documentation of informed consent will be completed prior to starting the study intervention.

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

We will obtain full written (either via paper-based or electronic signature) informed consent from patients enrolling in the study. Informed consent will occur via face-face discussion in clinic or via telemedicine between one of the study team members designated to perform informed consent and the potential study participant. The study member will explain the elements of the informed consent form including purpose, methods, extent of the study, risks, benefits, and alternatives to potential participants. Participants will be asked to read the consent form, given appropriate time to read the document on their own, and allowed to ask any questions prior to signing it. Consents will be written in simple, easy-to-understand language and obtained on the day of enrollment by one of the study team members designated to perform informed consent. 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 (either via paper-based informed consent or electronic signature of the REDCap-based electronic informed consent). All participants will receive a copy of their informed consent and HIPAA forms for their records (either a paper copy or an emailed copy). The informed consent process will take place in a private room in the Rutledge Tower Head and Neck Cancer Clinic, in a private room in the HCC, or the location that the patient is conducting the telemedicine clinic visit in cases of electronic informed consent. Only the study participant will provide informed consent. Subjects will be allowed up to one week to decide whether to participate in the study. Participants will also complete a HIPAA form at the same time using the same procedures as described above. All participants will receive a copy of their informed consent and HIPAA forms (either paper or emailed) for their records. Separate copies of the documents will be stored in the study binder under each patient's section.

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

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

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 AND QUALITY CONTROL

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

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

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

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

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

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

10.1.9 DATA HANDLING AND RECORD KEEPING

10.1.9.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection will be the responsibility of the clinical trial staff at the site under the supervision of the site investigator. The investigator will be responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All source documents will be completed in a neat, legible manner to ensure accurate interpretation of data.

Hardcopies of the study visit worksheets will be provided for use as source document worksheets for recording data for each participant consented/enrolled in the study. Data recorded in the electronic case report form (eCRF) derived from source documents will be consistent with the data recorded on the source documents.

Clinical data 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, MPH, FACS. 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 9. Abbreviations and Special Terms	
AE	Adverse Event
CFR	Code of Federal Regulations
CMP	Clinical Monitoring Plan
COC	Certificate of Confidentiality
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DSMB	Data Safety Monitoring Board
DRE	Disease-Related Event
EC	Ethics Committee
eCRF	Electronic Case Report Forms
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FFR	Federal Financial Report
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
GWAS	Genome-Wide Association Studies
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICH	International Council on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IDE	Investigational Device Exemption
IND	Investigational New Drug Application
IRB	Institutional Review Board
ISM	Independent Safety Monitor
ITT	Intention-To-Treat
LSMEANS	Least-squares Means

MedDRA	Medical Dictionary for Regulatory Activities
MOP	Manual of Procedures
NCT	National Clinical Trial
NIH	National Institutes of Health
NIH IC	NIH Institute or Center
OHRP	Office for Human Research Protections
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SMC	Safety Monitoring Committee
SOA	Schedule of Activities
SOC	System Organ Class
SOP	Standard Operating Procedure
THANC	Thyroid Head and Neck Cancer
UP	Unanticipated Problem
US	United States

10.4 PROTOCOL AMENDMENT HISTORY

Table 10. Protocol Amendment History

Version	Date	Description of Change	Brief Rationale
2.0	3/10/2020	Title SoA Endpoints: added IMAGE-HN, EORTC Inclusion Criteria: added cutaneous and salivary gland Sample Size: up to 48	Grammar Harmonize w/ eCRF Novel measures Inclusively target population Revised effect size of AC
3.0	8/9/20	Investigator signature page Screening, recruitment, and informed consent	Change of study team COVID-19 related changes to clinic workflow necessitating telemedicine recruitment and electronic informed consent
4.0	10/1/21	Sample size to 52 clarify certain exclusion criteria should have been described as criteria for study discontinuation	Larger than expected proportion of patients meeting criteria for study discontinuation due to cancer recurrence/2nd cancers Recognition that inclusion/exclusion criteria are determined at the time of accrual

11 REFERENCES

1. Jansen F, Snyder CF, Leemans CR, Verdonck-de Leeuw IM. Identifying cutoff scores for the EORTC QLQ-C30 and the head and neck cancer-specific module EORTC QLQ-H&N35 representing unmet supportive care needs in patients with head and neck cancer. Head Neck 2016; 38 Suppl 1:E1493-1500.

2. Murphy BA, Ridner S, Wells N, Dietrich M. Quality of life research in head and neck cancer: a review of the current state of the science. Crit Rev Oncol Hematol 2007; 62:251-267.

3. Fingeret MC, Vidrine DJ, Reece GP, Gillenwater AM, Gritz ER. Multidimensional analysis of body image concerns among newly diagnosed patients with oral cavity cancer. Head Neck 2010; 32:301-309.

4. Fingeret MC, Yuan Y, Urbauer D, Weston J, Nipomnick S, Weber R. The nature and extent of body image concerns among surgically treated patients with head and neck cancer. Psychooncology 2012; 21:836-844.

5. Rhoten BA. Body image disturbance in adults treated for cancer - a concept analysis. J Adv Nurs 2016; 72:1001-1011.

6. Teo I, Fronczyk KM, Guindani Met al. Salient body image concerns of patients with cancer undergoing head and neck reconstruction. Head Neck 2016; 38:1035-1042.

7. Rhoten BA, Murphy B, Ridner SH. Body image in patients with head and neck cancer: a review of the literature. Oral Oncol 2013; 49:753-760.

8. Fingeret MC, Teo I, Goettsch K. Body image: a critical psychosocial issue for patients with head and neck cancer. Curr Oncol Rep 2015; 17:422.

9. Hopwood P, Fletcher I, Lee A, Al Ghazal S. A body image scale for use with cancer patients. Eur J Cancer 2001; 37:189-197.

10. Cash TF, Santos MT, Williams EF. Coping with body-image threats and challenges: validation of the Body Image Coping Strategies Inventory. J Psychosom Res 2005; 58:190-199.

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

12. Cohen EE, LaMonte SJ, Erb NLet al. American Cancer Society Head and Neck Cancer Survivorship Care Guideline. CA Cancer J Clin 2016; 66:203-239.

13. Katz MR, Irish JC, Devins GM, Rodin GM, Gullane PJ. Psychosocial adjustment in head and neck cancer: the impact of disfigurement, gender and social support. Head Neck 2003; 25:103-112.

14. Millsopp L, Brandom L, Humphris G, Lowe D, Stat C, Rogers S. Facial appearance after operations for oral and oropharyngeal cancer: a comparison of casenotes and patient-completed questionnaire. Br J Oral Maxillofac Surg 2006; 44:358-363.

15. Rhoten BA, Deng J, Dietrich MS, Murphy B, Ridner SH. Body image and depressive symptoms in patients with head and neck cancer: an important relationship. Support Care Cancer 2014; 22:3053-3060.

16. Manne S, Badr H. Intimacy and relationship processes in couples' psychosocial adaptation to cancer. Cancer 2008; 112:2541-2555.

17. Osazuwa-Peters N, Simpson MC, Zhao Let al. Suicide risk among cancer survivors: Head and neck versus other cancers. Cancer 2018; 124:4072-4079.

18. Huang S, Liu HE. Effectiveness of cosmetic rehabilitation on the body image of oral cancer patients in Taiwan. Support Care Cancer 2008; 16:981-986.

19. Chen SC, Huang BS, Lin CYet al. Psychosocial effects of a skin camouflage program in female survivors with head and neck cancer: A randomized controlled trial. Psychooncology 2017; 26:1376-1383.

20. Giuliani M, McQuestion M, Jones Jet al. Prevalence and nature of survivorship needs in patients with head and neck cancer. Head Neck 2016; 38:1097-1103.

21. Jarry JL, Ip K. The effectiveness of stand-alone cognitive-behavioural therapy for body image: a meta-analysis. Body Image 2005; 2:317-331.

22. Jarry JL, Berardi K. Characteristics and effectiveness of stand-alone body image treatments: a review of the empirical literature. Body Image 2004; 1:319-333.

23. Fingeret MC, Teo I, Epner DE. Managing body image difficulties of adult cancer patients: lessons from available research. Cancer 2014; 120:633-641.

24. Przezdziecki A, Sherman KA, Baillie A, Taylor A, Foley E, Stalgis-Bilinski K. My changed body: breast cancer, body image, distress and self-compassion. Psychooncology 2013; 22:1872-1879.

25. Semple C, Parahoo K, Norman A, McCaughan E, Humphris G, Mills M. Psychosocial interventions for patients with head and neck cancer. Cochrane Database Syst Rev 2013:CD009441.

26. Eldredge L, Markham C, Ruiter R, Fernandez ME, Kok G, Parcel G. Planning Health Promotion Interventions: An Intervention Mapping Approach. San Francisco, CA: Jossey-Bass, 2016.

27. Ellis MA, Sterba KR, Day TAet al. Body Image Disturbance In Surgically-Treated Head and Neck Cancer Patients: A Patient-Centered Approach. Otolaryngol Head Neck Surg Accepted.

28. van Beugen S, Ferwerda M, Hoeve Det al. Internet-based cognitive behavioral therapy for patients with chronic somatic conditions: a meta-analytic review. J Med Internet Res 2014; 16:e88.

29. David JM, Ho AS, Luu Met al. Treatment at high-volume facilities and academic centers is independently associated with improved survival in patients with locally advanced head and neck cancer. Cancer 2017; 123:3933-3942.

30. Graboyes EM, Ellis MA, Li Het al. Racial and Ethnic Disparities in Travel for Head and Neck Cancer Treatment and the Impact of Travel Distance on Survival. Cancer 2018; 124:3181-3191.

31. Implementing Cancer Survivorship Care Planning. Washington, DC: National Academies Press, 2007.

32. Burris JL, Andrykowski M. Disparities in mental health between rural and nonrural cancer survivors: a preliminary study. Psychooncology 2010; 19:637-645.

33. Allison PJ, Edgar L, Nicolau B, Archer J, Black M, Hier M. Results of a feasibility study for a psycho-educational intervention in head and neck cancer. Psychooncology 2004; 13:482-485.

34. Budhrani-Shani P, Chau NG, Berry DL. Psychosocial distress and the preferred method of delivery of mind-body interventions among patients with head-and-neck cancer. Patient Relat Outcome Meas 2018; 9:129-136.

35. Wootton R, Bahaadinbeigy K, Hailey D. Estimating travel reduction associated with the use of telemedicine by patients and healthcare professionals: proposal for quantitative synthesis in a systematic review. BMC Health Serv Res 2011; 11:185.

36. Doolittle GC, Spaulding AO. Providing Access to Oncology Care for Rural Patients via Telemedicine. J Oncol Pract 2006; 2:228-230.

37. Agnisarman SO, Chalil Madathil K, Smith K, Ashok A, Welch B, McElligott JT. Lessons learned from the usability assessment of home-based telemedicine systems. Appl Ergon 2017; 58:424-434.

38. Andersson G, Cuijpers P, Carlbring P, Riper H, Hedman E. Guided Internet-based vs. face-to-face cognitive behavior therapy for psychiatric and somatic disorders: a systematic review and meta-analysis. World Psychiatry 2014; 13:288-295.

39. Graboyes EM, Maurer S, Park Yet al. Evaluation of a Novel Telemedicine-Based Intervention to Manage Body Image Disturbance in Head and Neck Cancer Survivors. Psychooncology 2020.

40. Rubinstein L, Crowley J, Ivy P, Leblanc M, Sargent D. Randomized phase II designs. Clin Cancer Res 2009; 15:1883-1890.

41. Vickers AJ, Ballen V, Scher HI. Setting the bar in phase II trials: the use of historical data for determining "go/no go" decision for definitive phase III testing. Clin Cancer Res 2007; 13:972-976.

42. Ratain MJ, Sargent DJ. Optimising the design of phase II oncology trials: the importance of randomisation. Eur J Cancer 2009; 45:275-280.

43. Graboyes EM, Hill EG, Marsh CH, Maurer S, Day TA, Sterba KR. Body Image Disturbance in Surgically-Treated Head and Neck Cancer Patients: A Prospective Cohort Pilot Study. Otolaryngol Head Neck Surg Accepted.

44. Ellis MA, Sterba KR, Brennan EAet al. A Systematic Review of Patient-Reported Outcome Measures Assessing Body Image Disturbance in Patients with Head and Neck Cancer. Otolaryngol Head Neck Surg 2019; 160:941-954.

45. Ellis MA, Sterba KR, Day TAet al. Body Image Disturbance in Surgically Treated Head and Neck Cancer Patients: A Patient-Centered Approach. Otolaryngol Head Neck Surg 2019; 161:278-287.

46. Kissane DW, Patel SG, Baser REet al. Preliminary evaluation of the reliability and validity of the Shame and Stigma Scale in head and neck cancer. Head Neck 2013; 35:172-183.

47. Pilkonis PA, Choi SW, Reise SPet al. Item banks for measuring emotional distress from the Patient-Reported Outcomes Measurement Information System (PROMIS(R)): depression, anxiety, and anger. Assessment 2011; 18:263-283.

48. Hahn EA, DeWalt DA, Bode RKet al. New English and Spanish social health measures will facilitate evaluating health determinants. Health Psychol 2014; 33:490-499.

49. Cash TF, Melnyk SE, Hrabosky JI. The assessment of body image investment: an extensive revision of the appearance schemas inventory. Int J Eat Disord 2004; 35:305-316.

50. Graboyes EM, Hill EG, Marsh CH, Maurer S, Day TA, Sterba KR. Body Image Disturbance in Surgically Treated Head and Neck Cancer Patients: A Prospective Cohort Pilot Study. Otolaryngol Head Neck Surg 2019; 161:105-110.

51. Sherman KA, Przezdziecki A, Alcorso Jet al. Reducing Body Image-Related Distress in Women With Breast Cancer Using a Structured Online Writing Exercise: Results From the My Changed Body Randomized Controlled Trial. J Clin Oncol 2018; 36:1930-1940.

52. Esplen MJ, Wong J, Warner E, Toner B. Restoring Body Image After Cancer (ReBIC): Results of a Randomized Controlled Trial. J Clin Oncol 2018; 36:749-756.

53. Barnard J, Rubin DB. Miscellanea. Small-sample degrees of freedom with multiple imputation. Biometrika 1999; 86:948-955.

54. Rubin DB. Multiple imputation for nonresponse in surveys. John Wiley & Sons, 2004.

55. Roderick JAL. A Test of Missing Completely at Random for Multivariate Data with Missing Values. Journal of the American Statistical Association 1998; 83:1198-1202.

56. Lavori PW, Dawson R, Shera D. A multiple imputation strategy for clinical trials with truncation of patient data. Stat Med 1995; 14:1913-1925.

57. Schafer JL. Analysis of incomplete multivariate data. Boca Raton, FL: Chapman & Hall/CRC, 1997.