A Multi-Site, Parallel-Group, Randomized Clinical Trial Comparing a Brief Tele-Cognitive Behavioral Therapy Intervention (BRIGHT) with Attention Control for the Reduction of Body Image-Related Distress Among Head and Neck Cancer Survivors

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CONFIDENTIALITY STATEMENT

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PROTOCOL VERSION HISTORY

1.2 Schema: Updated to reflect changes to stratification variables for randomization (see **6.3** below) and more clearly illustrate study endpoints.

1.3 Schedule of Activities: Corrected erroneous omission of intervention session 6 from Schedule of Activities in Protocol v2.0 (8 December 2022). Addressed downstream ramifications to other aspects of the Schedule of Activities created by adding a column for intervention session 6.

5.4 Screen Failures: Clarified definition of screen failure and circumstances for re-screening.

6.2 Fidelity: Changed from 20% of sessions to 17% of sessions to harmonize with prior change from 5 to 6 intervention sessions.

6.3 Measures to Minimize Bias: Randomization and Blinding: Added free flap reconstruction (yes/no) as stratification variable for randomization. Protocol harmonized in sections **1.2 (Schema)**, **4.1 (Overall Design)** and **9.4.2 (Analysis of Primary Endpoint)**. Clarified blinding of investigators, patients, and outcome assessors.

8.2 Baseline Assessments: Added baseline patient self-report assessment of history of medication or counseling for mental health disorders (Y/N).

8.3 Endpoint and other Non-Safety Assessments: Added information about scoring all PROMIS measures using the T-distribution. Provided additional details about fidelity assessments.

8.4 Adverse Events and Serious Adverse Events: Updated definition of adverse events to align with best practices for psychological clinical trials. Provided additional detail about methods of collecting adverse event data.

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STATEMENT OF COMPLIANCE

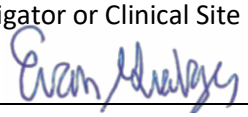
The trial will be conducted in accordance with International Council on Harmonisation Good Clinical Practice (ICH GCP), applicable United States (US) Code of Federal Regulations (CFR), and the National Cancer Institute (NCI) Terms and Conditions of Award. The Principal Investigator (PI) will assure that 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: 7/13/22

Name: Evan Graboyes
Title: A Multi-Site, Parallel-Group, Randomized Clinical Trial Comparing a Brief Tele-Cognitive Behavioral Therapy Intervention (BRIGHT) with Attention Control for the Reduction of Body Image-Related Distress Among Head and Neck Cancer Survivors

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1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title: A Multi-Site, Parallel-Group, Randomized Clinical Trial Comparing a Brief Tele-Cognitive Behavioral Therapy Intervention (BRIGHT) with Attention Control for the Reduction of Body Image-Related Distress Among Head and Neck Cancer Survivors

Grant Number: R37 CA269385

Study Description: In this multi-site, parallel-group, randomized clinical trial, we will evaluate the efficacy of BRIGHT compared with attention control (AC) for managing body image distress (BID) among head and neck cancer survivors (HNC) survivors, examine BRIGHT's underlying mechanisms, and characterize factors affecting the future adoption of BRIGHT into clinical care.

Objectives:

Primary Objective:
To evaluate the efficacy of BRIGHT compared with AC on HNC-related BID as measured by change from baseline in the IMAGE-HN score.

Secondary Objectives:
1. To evaluate the clinical response rate of BRIGHT compared with AC on HNC-related BID as measured by proportion of patients with a clinically meaningful change from baseline in the IMAGE-HN score.

2. To further evaluate the longer-term efficacy of BRIGHT compared with AC on HNC-related BID as measured by change from baseline in the IMAGE-HN score at 9-month follow-up (post-randomization).

3. To evaluate the efficacy of BRIGHT compared with AC on psychological and social well-being as measured by change from baseline in Shame and Stigma Scale in HNC, PROMIS SF v1.0-Depression 8a, PROMIS SF v1.0-Anxiety 8a, Beck Scale for Suicidal Ideation, and PROMIS SF v2.0-Ability to Participate in Social Activities-8a scores at 3-, 6-, and 9-month follow-up.

4. To evaluate the efficacy of BRIGHT compared with AC on quality of life (QOL) as measured by change from baseline in the EORTC QLQ-HN35 score at 3-, 6-, and 9-month follow-up.

5. To examine the mechanism of change underlying BRIGHT for HNC-related BID as measured by change from baseline in Body Image Coping Strategies Inventory subscale scores and the Automatic Thoughts Questionnaire score.

Endpoints:	Primary Endpoint: Change in the IMAGE-HN score from baseline to 6-month follow-up Select Secondary Endpoints: 1. Change in the IMAGE-HN score from baseline to 2-, 3- and 9-month follow-up 2. Proportion of patients with a decrease in the IMAGE-HN score of $\geq$ 9 points from baseline at 3-, 6-, and 9-month follow-up 3. Change in the Shame and Stigma Scale in HNC score from baseline to 3-, 6-, and 9-month follow-up 4. Change in the PROMIS SF v1.0-Depression 8a score from baseline to 3-, 6-, and 9-month follow-up 5. Change in the PROMIS SF v1.0-Anxiety 8a score from baseline to 3-, 6-, and 9-month follow-up 6. Change in the Body Image Coping Strategies Inventory Avoidance, Positive Rational Acceptance, and Appearance Fixing subscale scores from baseline to 2, 3-, and 6-month follow-up
Study Population:	The study population will consist of adult HNC survivors with HNC-related BID
Phase or Stage:	N/A
Description of Sites/Facilities Enrolling Participants:	The study will be conducted, and participants enrolled, at three sites: (1) the Medical University of South Carolina (MUSC), (2) Henry Ford Health, and (3) Washington University in St. Louis
Description of Study Intervention/Experimental Manipulation:	BRIGHT is 6 sessions of weekly, 60-minute, manualized individual tele-cognitive behavioral therapy based on a transactional coping model of HNC-related BID
Study Duration:	49 months
Participant Duration:	9 months

1.2 SCHEMA

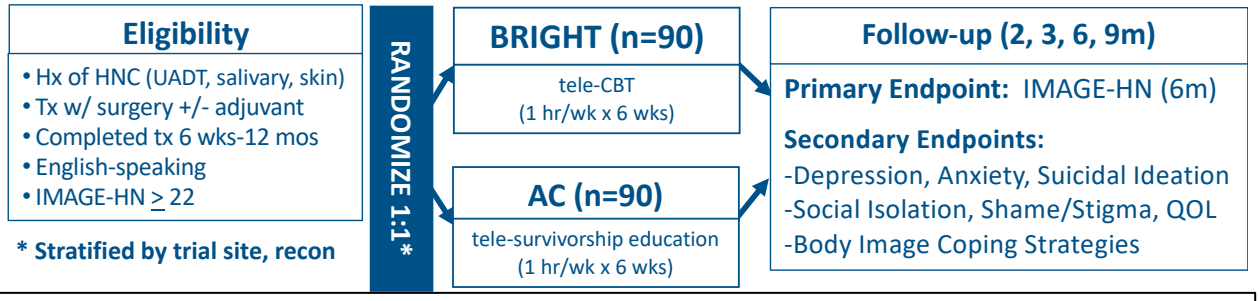


Fig 1. Schema. In this multisite RCT, HNC survivors with clinically significant HNC-related BID (N=180) from the Medical University of South Carolina (MUSC), Washington University School of Medicine (WUSM), and Henry Ford Health (HFH) will be randomized 1:1 to BRIGHT or AC with randomization stratified by site (MUSC, WUSM, HFH). Patients will complete measures of HNC-related BID (primary endpoint), psychological and social well-being, and mechanisms of change underlying CBT at 2, 3, 6, and 9-month follow-up (post-randomization) to assess the effect of BRIGHT on BID, psychological and social well-being and quality of life, and mechanism of change underlying BRIGHT.

1.3 SCHEDULE OF ACTIVITIES

Table 1. Schedule of Activities for BRIGHT and AC: Screening, Treatment, and Follow-up

Study Period		Screening	Allocation	Treatment						Follow-up[b]				For Details
Visit Label				Session						2 m	3 m	6 m	9 m	
				1	2	3	4	5	6					
Visit #		1[a]	--	2	3	4	5	6	7	8	9	10	11	
Study Activity														
Enrollment	Eligibility Screen[c]	X												*5*
	Informed Consent[d]	X												*9.5.2*
Allocation			X											
Study Intervention	BRIGHT			X	X	X	X	X	X					*6.1.1*
	AC			X	X	X	X	X	X					*6.1.2*
Study Assessments														
Baseline	Demographics	X												*8.2*
	Clinical and Oncologic	X												
Safety	Adverse Events			X	X	X	X	X	X	X	X	X	X	*8.4*
Concomitant Meds	Medication Assessment	X		X	X	X	X	X	X	X	X	X	X	*6.5*
Efficacy[e]	IMAGE-HN	X								X	X	X	X	*8.3.1*
	Shame and Stigma Scale	X								X	X	X	X	
	PROMIS SF v1.0-Depression 8a	X								X	X	X	X	
	PROMIS SF v1.0-Anxiety 8a	X								X	X	X	X	
	Beck Scale for Suicidal Ideation[f]	X								X	X	X	X	
	PROMIS SF v2.0-Social Activitites-8a	X								X	X	X	X	
	EORTC QLQ-HN35	X								X	X	X	X	
Mechanism	BICSI	X								X	X	X		*8.3.2*
	Automatic Thoughts Questionnaire	X								X	X	X		
Intervention Fidelity	BRIGHT Fidelity and Competence Scale									X				*8.3.3*
	Interventionist self-report			X	X	X	X	X	X					
Patient Adherence	Attendance, Homework			X	X	X	X	X	X					*8.3.4*
Common Factors	WAI-SR-Therapist								X					*8.3.3*
	Therapist Empathy Scale								X					
	Credibility/Expectancy Questionnaire	X							X					

Table 1. Schedule of Activities for BRIGHT and AC: Screening, Treatment, and Follow-up

Study Period	Screening	Allocation	Treatment						Follow-up[b]				For Details
Visit Label			Session						2 m	3 m	6 m	9 m	
			1	2	3	4	5	6					
Visit #	1[a]	--	2	3	4	5	6	7	8	9	10	11	

[a]: Every effort should be made to minimize the time between randomization and starting treatment
[b]: Study assessments are determined based on time since randomization. Follow-up study assessments should be completed +/-1 week from the indicated timing.
[c]: Eligibility assessed using information in the electronic health record as well as a screening IMAGE-HN
[d]: Written informed consent and HIPAA must be obtained prior to performing and protocol-specific procedures, including baseline evaluations.
[e]: 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, text message, 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.
[f]: Beck suicidality scale requires the program coordinator to monitor responses for suicidality via REDCap-based alert system and address accordingly as outlined in **section 2.3.3.**

Abbreviations: **AC:** Attention Control; **AE:** Adverse Event; **BICSI:** Body Image Coping Strategies Inventory; **BRIGHT:** Building a Renewed ImaGe after Head & neck cancer Treatment; **EORTC:** European Organisation for Research and Treatment of Cancer; **IMAGE-HN: I**nventory to **M**easure and **A**ssess ima**G**e disturbanc**E**-**H**ead & **N**eck; **PROMIS:** Patient-Reported Outcome Measurement Inventory System; **WAI-SR:** Working Alliance Inventory-Short Revised

2 INTRODUCTION

2.1 STUDY RATIONALE

Head and neck cancer (HNC) results in substantial life-altering morbidity related to disfigurement, difficulty swallowing, impaired smiling, and challenges speaking.[1,2] As a result, 75% of HNC survivors express body image concerns[3] and 28% meet criteria for body image-related distress (BID).[4] BID is a source of devastating psychosocial morbidity and functional impairment for HNC survivors, contributing to a six-fold increase in depression, high rates of social isolation, and decreased quality of life (QOL).[4-9] Due in part to BID, HNC survivors have a 2-fold higher rate of suicide mortality relative to other cancer survivors and a 4-fold higher rate than the general population.[10] Although it is critical that HNC survivors with BID have access to evidence-based care, a recent national survey found that management of BID was the single most commonly omitted component of HNC survivorship care.[11] Among HNC survivors with BID, trials evaluating interventions to conceal disfigurement[12,13] and improve self-compassion[14] showed that these strategies were ineffective. To date, theoretically grounded, evidence-based strategies to manage HNC-related BID are lacking.[15]

To address this gap, we developed BRIGHT (Building a Renewed ImaGe after Head & neck cancer Treatment),[16] a 6-session manualized tele-cognitive behavioral therapy (CBT) based on a transactional coping[17] model of HNC-related BID. Findings from our single-arm[16] and pilot randomized clinical trial (RCT) showed that BRIGHT was feasible, acceptable, and resulted in a statistically and clinically significant reduction in BID relative to dose- and delivery-matched attention controls (ACs) at 1- and 3-month post-intervention follow-up. There is consensus that evidence-based psychotherapy should be supported by theory-based mechanisms of change;[18,19] however, a gap remains in our understanding of mechanisms of change underlying CBT for BID.[20-24] Preliminary data suggest that BRIGHT reduces HNC-related BID by enhancing adaptive body image coping skills (reducing avoidance, increasing positive rational acceptance [i.e. rational appearance related self-talk]).[16] These promising data support further evaluation of BRIGHT's efficacy and mechanism in a large-scale RCT. Finally, recognizing the chronic evidence-to-practice gap that limits the delivery of psychosocial care to cancer survivors,[25] it is imperative that we concurrently identify strategies to enhance the future adoption of BRIGHT into routine care.

Herein we extend our initial research with a multisite, parallel-group, RCT we will evaluate the efficacy of BRIGHT compared with AC for managing BID among HNC survivors, examine BRIGHT's underlying mechanisms, and characterize factors affecting the future adoption of BRIGHT into clinical care. HNC survivors with clinically significant HNC-related BID[4] (N=180) will be randomized to BRIGHT or AC, a manualized tele-supportive care intervention that controls for professional attention, dose, delivery method, and common factors (alliance, empathy, expectations).[26] HNC survivors will complete the Inventory to Measure and Assess imaGe disturbancE14-Head & Neck (IMAGE-HN; a valid measure of HNC-related BID[27]), measures of psychological and social well-being and QOL, and measures of theory-derived mechanisms of change underlying BRIGHT at 2-, 3-, 6-, and 9-months post randomization. We will conduct semi-structured interviews and in-depth site visits to develop an implementation toolkit to enhance the adoption of BRIGHT into clinical care.

2.2 BACKGROUND

2.2.1 PREVALENCE OF BID AMONG HNC SURVIVORS

There are nearly 500,000 HNC survivors in the US[28] and this population is growing exponentially.[29] Standard of care treatment involves combinations of surgery, radiation, and chemotherapy to cosmetically and functionally critical areas such as the face, lips, tongue, teeth, jaw, and throat. As a result, treatment results in substantial life-altering morbidity related to facial disfigurement, difficulty swallowing, impaired smiling, and challenges speaking.[1] These treatment-related toxicities occur in highly visible, socially significant parts of the body and limit basic daily activities such as eating, engaging in conversation, being understood by others, and participating in social interactions.[5-7] As a result of these impairments in communication, interpersonal relationships, and self-concept, 75% of HNC survivors express body image concerns[3] and 20-28% have clinically significant BID.[4,30]

2.2.2 CONSEQUENCES OF BID AMONG HNC SURVIVORS

HNC survivors with BID suffer devastating psychosocial morbidity and reduced QOL.[5-7] Relative to HNC survivors without BID, those with BID have a six-fold increase in moderate-severe depressive symptoms and an eight-fold increase in moderate-severe anxiety symptoms.[4] HNC-related BID also drives impairments in social and relationship functioning by increasing social anxiety, social isolation, and feelings of stigmatization.[31] In addition, HNC-related BID exacerbates financial toxicity, as HNC survivors with BID are more likely to discontinue employment and be unemployed or on disability.[8,9] Finally, due in part to BID, HNC survivors have a 2-fold higher rate of suicide mortality relative to other cancer survivors and a 4-fold higher rate than the general population.[10] BID among HNC survivors is common, causes significant psychosocial morbidity, and is a key contributor to decreased QOL; treatment for BID should be widely available to HNC survivors.

2.2.3 LONGITUDINAL COURSE OF BID AMONG HNC SURVIVORS

Most studies of BID among HNC survivors have either been cross-sectional[6,32-36] or included only short-term follow-up.[37,38] In one prospective cohort study using a purposive sample of 68 patients with HNC, patients completed the Body Image Scale[39] pretreatment and 1, 3, 6, 9, and 12-months post-treatment. Change in Body Image Scale score (higher score indicates worse BID) relative to pretreatment were analyzed with a linear mixed model. 43% of patients had persistently elevated Body Image Scale score 9-months after HNC treatment.[40] In this subset of patients, the mean change in Body Image Scale score remained elevated at all timepoints for the first year post-treatment relative to baseline (**Figure 2**).[40] These findings suggest that nearly four in ten HNC survivors experience BID that persists for at least 1 year post-treatment without any spontaneous improvement.[40]

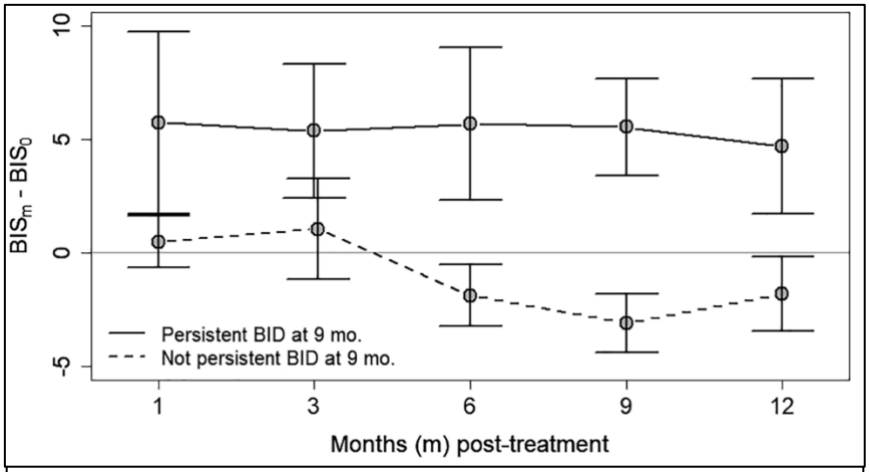


Fig 2. Temporal Trajectory of BID Among HNC Survivors. Changes in the severity of BID (as determined by the mean change in Body Image Scale score at each post-treatment time point relative to baseline, stratified by those with or without persistent elevation of Body Image Scale scores at 9 months post-treatment.

2.2.4 PRIOR INTERVENTIONS TO MANAGE BID AMONG HNC SURVIVORS

Evidence-based strategies to manage BID among HNC survivors are lacking.[5] To date, three trials have evaluated different strategies to manage HNC-related BID. Huang et al. showed that a cosmetic rehabilitation intervention did not improve BID among HNC survivors relative to control ($p>0.05$).[12] An RCT by Chen et al. evaluating a skin camouflage program among HNC survivors found no benefit relative to usual care ($p=0.56$).[13] Finally, a single-arm pre-post study showed that MyChangedBody (MyCB), a web-based self-compassion expressive writing activity, failed to improve HNC-related BID ($p=0.73$).[14] The lack of efficacy of MyCB among HNC survivors with BID is important because MyCB improved BID among breast cancer survivors in a large RCT (N=304) relative to control ($p=0.035$).[41] These trials (1) reinforce the need to develop effective strategies to improve BID among HNC survivors and (2) motivate shifting the paradigm away from concealing disfigurement and enhancing self-compassion in favor of a fundamentally different approach that addresses the causal mechanisms underlying BID among HNC survivors.

2.2.5 RATIONALE FOR A CBT-BASED APPROACH TO MANAGE HNC-RELATED BID

CBT is a promising approach to manage HNC-related BID. Multiple meta-analyses have demonstrated that CBT produces durable reductions in BID in patients without visible disfigurement (e.g., eating disorders, body dysmorphic disorder).[42-45] However, the evidence base supporting CBT for BID in patients with visible disfigurement is much weaker.[46-48] Whereas some studies have suggested that CBT may reduce BID among patients with disfigurement (e.g., facial burns, craniofacial disorders, breast cancer),[49-52] two recent systematic reviews noted significant methodologic limitations in these studies including small sample size, non-randomized allocation, and comparison to waitlist control.[53,54] These findings underscore the need for rigorous trials evaluating the efficacy of CBT as novel paradigm to manage BID for HNC survivors.

Operating within David's integrative cognitive psychology model of human feelings and behaviors,[19] we conceptualize HNC-related BID according to Folkman's transactional theory of stress and coping.[17,24,46,55] According to our model, when a HNC survivor is confronted with a body image stimulus that may result in distress such as being invited to eat dinner with a friend at a restaurant, she attends to the stimulus, appraises it via automatic thoughts related to body image self-evaluation, and generates body image-related emotional, cognitive, and behavioral responses. When the body image response is negative, the HNC survivor utilizes a body image coping strategy to regulate the distress. Based on work by our team[56] and others,[24,46] the underlying mechanisms causing HNC-related BID are (1) unhelpful automatic thoughts and (2) maladaptive body image coping skills. In our example, a HNC survivor with BID may have an unhelpful automatic thought that *everyone* at the restaurant will notice and react negatively to her asymmetric face and drooling (e.g., a cognitive distortion of fortune-telling). A HNC survivor may attempt to cope with this stressor using a maladaptive body image coping strategy of avoidance and stay at home instead of going to eat at the restaurant with her friend. Together unhelpful automatic thoughts and maladaptive body image coping strategies initiate and maintain HNC-related BID. HNC survivors are unique in their experience of disfigurement and function-related impairment that is noticed and reacted to negatively by others through actions such as staring.[56,57] Thus for HNC survivors, the experience of distressing body image-related emotions is based in part in reality instead of being driven solely by unhelpful automatic thoughts, the dominant causal mechanism for patients with BID and no visible disfigurement.[24] As a result, a CBT paradigm for HNC survivors with BID should target body image coping skills in addition to unhelpful automatic body image thoughts.

2.2.6 MECHANISM OF CHANGE UNDERLYING CBT FOR BID

The mechanisms of change underlying CBT for BID are poorly characterized. As interventions to manage HNC-related BID are developed, it is essential to evaluate the underlying theoretical mechanism of change to (1) avoid pseudoscientific interventions, (2) optimize the effectiveness of treatment, and (3) advance the science of CBT broadly by identifying psychological factors involved in pathology and health which the therapeutic package targets.[18,19] Although CBT is effective at managing BID,[42-45] very little is known about underlying theory-based mechanisms of change, particularly among patients with visible disfigurement.[24] Many trials evaluating CBT for BID among patients with disfigurement have not been theory-driven and thus did not evaluate the mechanisms of change at all.[49-52] Limited correlational and clinical trial data suggest that CBT for BID (1) enhances adaptive body image coping strategies such as positive rational acceptance (i.e., rational appearance related self-talk) and (2) decreases maladaptive body image coping strategies such as avoidant coping.[46,48,58-61] However, these studies are limited by the absence of underlying theory, small sample size, unclear temporal precedence of the mediator, and lack of formal mediation analyses. Furthermore, they fail to evaluate mechanisms of change underlying various forms of CBT (e.g., automatic thoughts [cognitive therapy], unconditional self-acceptance [rational emotive behavioral therapy]).[19,62] Collectively, these data show that our understanding of the role of body image coping strategies and theory-based mechanisms of change underlying CBT for BID remains extremely limited, and thus rigorous clinical trial theory[18] testing is necessary.

2.2.7 RATIONALE FOR TELEMEDICINE DELIVERY PLATFORM

Cancer survivors face unique access-to-care barriers for face to face psychosocial care.[63] For patients with HNC, travel burden (due to the regionalization of HNC care[64,65]) is a critical barrier to mental health care and contributes to excess morbidity and mortality.[66,67] 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 psychosocial interventions to HNC survivors are needed.[68,69] Telemedicine is a promising solution because it decreases travel burden[70], increases access to care[71], and provides effective behavioral health interventions[72] (including CBT[63,73]). 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.[16]

2.2.8 DEVELOPMENT OF BRIGHT

The lack of effective interventions to manage BID among HNC survivors[12-14] and persistence of clinically significant BID[40] confirm the need to develop novel strategies to manage BID. BRIGHT was developed using Intervention Mapping.[74] We included extensive stakeholder engagement; N=22 HNC survivors completed semi-structured interviews to inform the content of BRIGHT.[56] Patients in our cohort study[37] also completed a quantitative needs assessment to inform the delivery of BRIGHT. BRIGHT is situated within a cognitive psychology perspective[19] of BID and conceptualizes HNC-related BID according to Folkman's transactional theory of stress and coping.[17,24,46,55] Our qualitative work identified key domains of HNC-related BID that informed the content of BRIGHT: personal dissatisfaction with appearance, other-oriented appearance concerns, distress with functional impairments, and social avoidance.[56] Stakeholder feedback from HNC survivors and clinicians helped define BRIGHT's timing (early post-treatment), setting (one-on-one therapy), duration (limited number of sessions), and delivery method

(telemedicine). Our conceptual model of BRIGHT is shown in **Figure 3**.

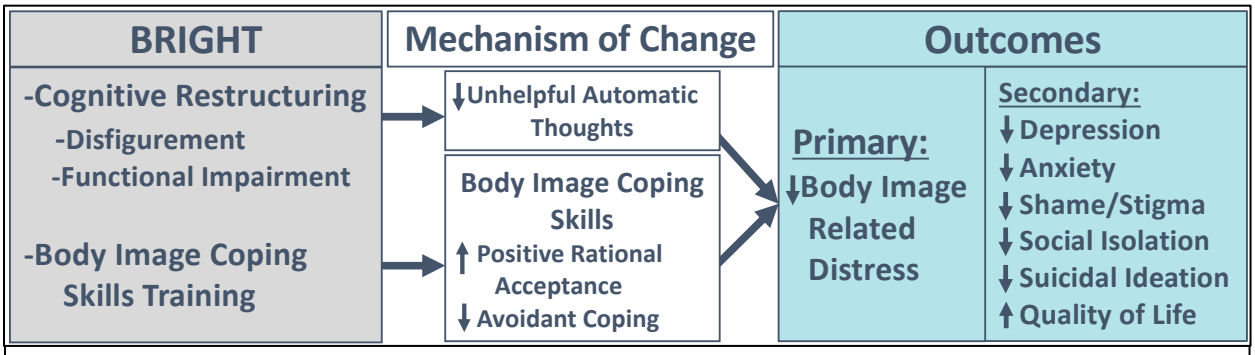


Fig 3. Conceptual Model of BRIGHT. BRIGHT is a cognitive therapy whose therapeutic package (cognitive restructuring of dysfunctional body image thoughts, body image coping skills training [gray box]) targets the underlying theory-based mechanism of the disorder (unhelpful automatic thoughts related to body image, maladaptive body image coping strategies; mechanisms of change [white box]), thereby decreasing BID and downstream psychosocial morbidity (clinical outcomes [teal box]).

2.2.9 FEASIBILITY AND ACCEPTABILITY OF BRIGHT

Feasibility and acceptability of BRIGHT was initially evaluated in our 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**).[16]

Table 2. BRIGHT Feasibility and Acceptability: Single-arm pilot trial

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)
Tablet returned to study team after BRIGHT, n (%)	10 (100)
Study dropout, n (%)	1 (10)
Acceptability to Patients (Program Evaluation)	**Mean (SD)[a]**
How well did the timing of the program work for you?	4.4 (0.7)
How well did the method of program delivery work?	4.7 (0.5)
How well did the number of sessions work for you?	4.6 (0.5)
How relevant was the content of each session?	4.6 (0.3)
Session 1	4.1 (1.3)
Session 2	4.4 (0.7)
Session 3	4.6 (0.5)
Session 4	4.9 (0.3)
Session 5	4.8 (0.4)
How likely are you to recommend BRIGHT?	4.9 (0.3)
[a]Scale 0-5; higher score indicates greater satisfaction.	

Feasibility and acceptability of BRIGHT were subsequently evaluated in our single-site pilot RCT (NCT03831100). Of the 252 patients screened over a 17-month period, 24.6% (n=62) met eligibility criteria and 87% (n=54) of eligible patients accrued to the trial. Six percent of randomized patients (n=3) dropped out of the study and 13% (n=7) went off study per protocol after developing a recurrence or new primary cancer. The remaining 82% of patients (n=44) completed BRIGHT or AC as allocated, of whom 96% (42/44) completed follow-up assessments as 1-week and 100% (44/44) completed assessments at 1-month and 3-months post-intervention (0% lost to follow-up).

Patients in BRIGHT rated the timing of the intervention relative to HNC treatment, method of delivery, content, workbook, homework, and relevance of the material highly (all mean ≥ 4/5/5) (**Table 3**). Overall, 75% of patients (15/20) reported that they were highly likely to recommend BRIGHT to other HNC survivors with BID.

Table 3. BRIGHT Acceptability: Single-Site Pilot RCT

Measure	Mean (SD)[a]
The timing of the program worked well for me.	4.5 (0.8)
The method of program delivery (telemedicine) worked well for me.	4.5 (0.9)
The number of sessions (5) worked well for me.	4.2 (1.2)
The content of each session was helpful to me.	4.7 (0.6)
The BRIGHT Workbook was useful to me.	4.5 (0.7)
The BRIGHT Homework assignments were useful.	4.5 (0.6)
The in-session activities were useful.	4.8 (0.4)
The material was relevant to my concerns.	4.7 (0.9)
Overall, I was satisfied with the BRIGHT Program.	4.7 (0.5)
I am likely to recommend BRIGHT to a different head and neck cancer survivor.	4.7 (0.6)

[a] Scores range from 0-5; higher values representing greater satisfaction or stronger agreement.

2.2.10 PRELIMINARY EFFECT OF BRIGHT ON BID

In our single-arm pilot trial, BRIGHT demonstrated high levels of clinical activity at reducing BID among HNC survivors.[16] Eighty-nine percent of participants (8/9) experienced a decrease in their Body Image Scale score from baseline to 1-month post-BRIGHT.[16] The clinical effect of BRIGHT on BID was large (**Figure 4**); BRIGHT was associated with a mean decrease of 4.56 in the BIS score from baseline to 1-month post intervention (95% CI 1.55, 7.56).[16] This clinical effect on BID persisted at 3 months post-BRIGHT relative to baseline (mean of the difference of the BIS score from baseline to 3-months post = 3.56; 95% CI 1.15 to 5.96).[16]

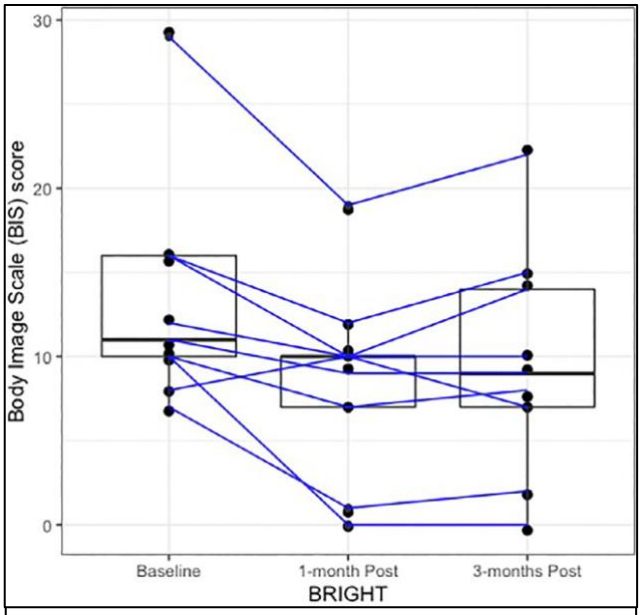


Fig 4. Decrease in the severity of BID (as determined by Body Image Scale scores) at 1- and 3-months post-BRIGHT relative to baseline. The mean Body Image Scale scores at baseline, 1-month post, and 3-month post are 13.22, 8.67, and 9.76, respectively.

In a subsequent single-site pilot RCT comparing BRIGHT with dose and delivery-matched AC (survivorship video educational materials), BRIGHT showed continued efficacy at improving BID among HNC survivors.[75] At 1-month post-intervention, the mean change from baseline in the IMAGE-HN score was significantly improved for patients in BRIGHT compared with patients in AC (mean model-based difference in change in the IMAGE-HN score = -7.9 [90% CI, -15.9 to 0.0] points; $P = 0.10$).[75] At 3-months post-intervention, BRIGHT improved the IMAGE-HN score from baseline relative to AC (mean model-based difference in change in IMAGE-HN score = -17.1 [90% CI, -25.6 to -8.6] points; $P = 0.002$).[75] At 3 months post-intervention, the improvement from baseline in the IMAGE-HN score for BRIGHT relative to AC was

clinically significant and corresponded to a large effect size (Cohen's *d* = -0.9 [90% CI, -1.4 to -0.4]).[75] The longitudinal change in HNC-related BID, as measured by change in the IMAGE-HN score from baseline, for patients allocated to BRIGHT and AC is shown in **Figure 5A**.

BRIGHT was effective at reducing HNC-related BID for the majority of patients. The waterfall plot demonstrating each patient's clinical response to BRIGHT or AC, as measured by change in IMAGE-HN scores from baseline to 3-months post-intervention, is shown in **Figure 5B**. At 3-months post-intervention, patients in BRIGHT had a 6.6-fold increase in the odds of clinical response (proportion of patients with a clinically meaningful decrease in IMAGE-HN scores of $\geq$ 9) relative to patients in AC (model-based odds ratio [OR] = 6.6 [90% CI, 2.0 to 21.8]; *p* = 0.09).[75]

Mean Change from Baseline and Response of Head and Neck Cancer (HNC)-Related Body Image Distress for Patients in BRIGHT and Attention Control

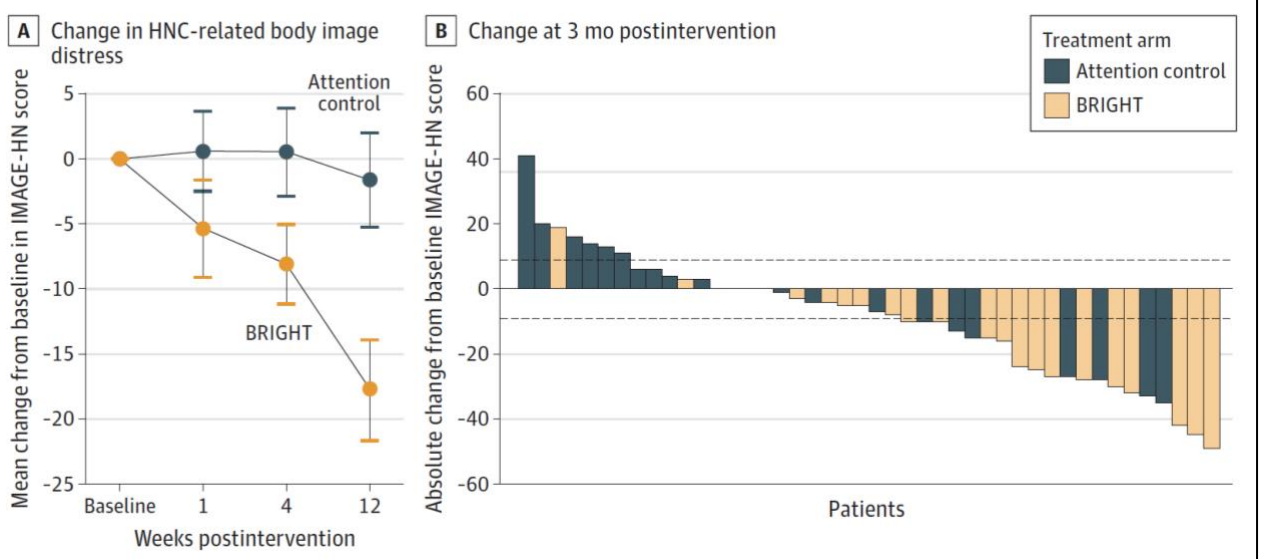


Fig 5. A. Line graph demonstrating the mean change from baseline in IMAGE-HN scores over time by intervention allocation. Error bars represent 1 SE above and below the mean. **B.** Waterfall plot showing response to BRIGHT and Attention control, as measured by absolute change from baseline in IMAGE-HN scores at 3 months postintervention. IMAGE-HN scores range from 0 to 84, with higher scores indicating worse HNC-related BID (and negative bars thus indicating improvement in HNC-related BID). The dashed horizontal line at +/- 9 indicates a clinically meaningful change in IMAGE-HN score.

2.2.11 PRELIMINARY EFFECT OF BRIGHT ON OTHER PSYCHOSOCIAL OUTCOMES AND QOL

In our single-arm pilot trial, BRIGHT was associated with improvements in psychosocial aspects of HNC-related QOL in our single-arm pilot trial of BRIGHT.[16] 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 European Organisation for Research and Treatment of Cancer (EORTC) QLQHN35 (median trouble with social eating scores = 66.67, 45.83, and 25, at baseline, 1-, and 3- months post-BRIGHT respectively; **Figure 6**).[16] 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).[16]

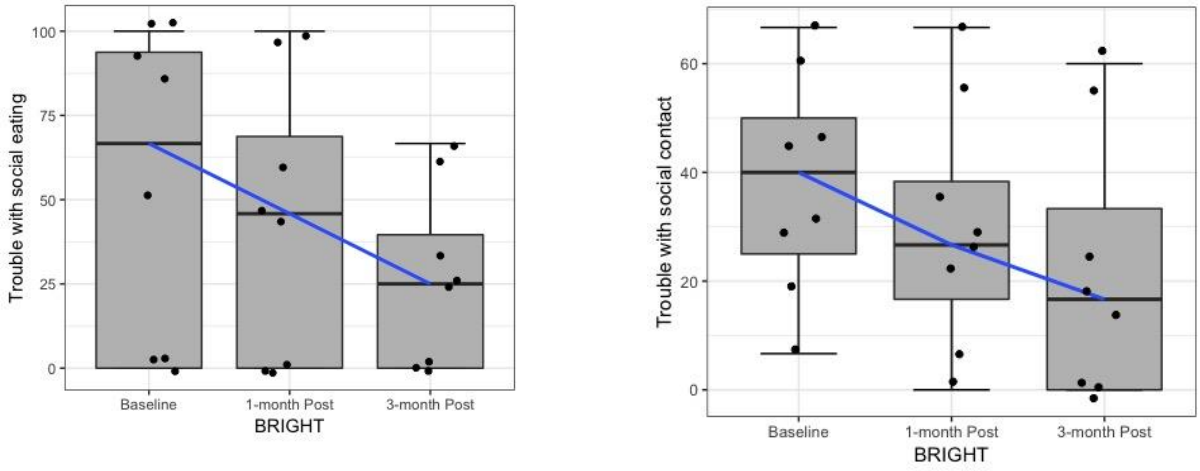


Fig. 6. A. Decrease in difficulty with social eating (as determined by EORTC QLQ-H&N35 Trouble with Social Eating Subscale scores) at 1- and 3-months post-BRIGHT relative to baseline. **B.** Decrease in difficulty with social contact (as determined by EORTC QLQ-H&N35 Trouble with Social Contact Subscale scores) at 1- and 3-months post-BRIGHT relative to baseline

2.2.12 PRELIMINARY MECHANISM OF BRIGHT

Preliminary data from our single-arm and pilot RCT suggest that BRIGHT decreased BID by enhancing body image coping strategies. During semi-structured interviews, HNC survivors from our single-arm trial described how BRIGHT decreased HNC-related BID by improving body image coping skills (**Table 4**).[16] Preliminary analysis of pilot RCT data showed that the treatment effect of BRIGHT on BID was mediated by enhancing adaptive body image coping skills such as positive rational acceptance (indirect effect = -0.96; 95% CI -4.79 to 1.24) and decreasing maladaptive body image coping skills such as avoidance (indirect effect 3.91; 95% CI -0.50 to 9.93). Although the quantitative analyses are exploratory and underpowered to detect a causal mediation relationship, these data suggest that (1) BRIGHT enhances adaptive body image coping skills and (2) these improvements in body image coping skills mediate improvements in HNC-related BID. In the pilot RCT, therapeutic alliance between the patient and BRIGHT therapist was not correlated with change in IMAGE-HN score from baseline to 3-months post-intervention (r= -0.06; p=0.77 for Working Alliance Inventory-Short Revised (WAI-SR) Client[76]).

Table 4. BRIGHT Enhances Adaptive Body Image Coping Skills: Representative Quotations from Semi-Structured Interviews[16]

"I used the tools I learned during BRIGHT to get the courage to take a trip to visit my son…and held it together when others stared at me." (ID 2)
"BRIGHT brought attention to thinking about myself rather than just feeling sorry for myself." (ID 3)
"BRIGHT gave me new tools to help cope with things that I didn't know how to think about…being grounded with image issues when I have to go out in public to have the courage to do it and know how to cope with it." (ID 4)
"BRIGHT helped me handle uncomfortable situations to get back to activities." (ID 8)
"BRIGHT gave me a lot of smart idea, thoughts, techniques for how to deal with things and what to think about my body and the surgery." (ID 9)

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 and single-site pilot RCT comparing BRIGHT with AC were minimal risk studies that were approved by the Medical University of South Carolina (MUSC) Institutional Review Board (IRB) under an expedited review (45CFR46.110). The proposed study will use a single IRB structure with MUSC serving as the IRB of record. No formal Data and Safety Monitoring Board was required in the prior studies of BRIGHT, although a Data and Safety Monitoring Plan (DSMP) with principal investigator (PI) and IRB-based oversight was created. The main study procedures include (1) either BRIGHT (CBT) or AC (a manualized tele-supportive care intervention that controls for professional attention, dose, delivery method, and common factors) and (2) completion of study questionnaires. These are generally considered minimal risk activities, although one of the questionnaires inquires about suicidal ideation. There are no physical, financial, legal, social, or cultural, risks to the study participants by joining this study. The primary risks of the study associated with the intervention or study assessments include psychological/emotional distress and breach of privacy/confidentiality.

Psychological/emotional distress: Subjects may experience adverse psychological reactions such as anxiety, depression, stress, distress, or suicidal ideation 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 experience with prior similar trials, we expect only minimal risk to participants. Nevertheless, we have a specific protocol to address situations in which a patient becomes distressed as a result of either the study intervention or study assessments. The project coordinator and all of the study interventionists have extensive experience dealing with this patient population and appropriate safeguards have been put in place to mitigate against this risk in either situation. There is a licensed clinical psychologist at each site that is trained in assessing and intervening upon distress.

Breach of privacy/confidentiality: There is also a risk that confidential information about the participant may be accidentally disclosed to non-study personnel, resulting in loss of privacy and potential risk to reputation. The risk is estimated to be extremely 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. However, records which identify subjects such as the signed informed consent document may be inspected by the NIH/NCI and the MUSC IRB. In addition, if it were learned that the patient is a danger to her/himself or others, then appropriate authorities would be notified, as required by law. Because of the need to release information to these parties, absolute confidentiality cannot be guaranteed, but the risk of accidental breach of confidentiality is extremely low.

2.3.2 KNOWN POTENTIAL BENEFITS

Based on our pilot data about the clinical impact of BRIGHT on BID[16], we hypothesize that participants in the BRIGHT arm will have a clinically significant reduction in the severity of their BID as well as improvement in their psychological and social well-being and QOL. However, although we hypothesize a direct benefit to participants in the BRIGHT arm (in terms of BID, psychological, and social well-being and QOL), 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 CBT interventions may help treat BID in cancer survivors.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

The adequacy of protection against potential risks and assessment of potential risks and benefits is described below.

Informed Consent. We will obtain full written informed consent from patients prior to enrolling in the study. Informed consent will occur via face-face discussion between one of the study team members designated to perform informed consent and the potential study participant. The study team member will explain to potential participants the elements of the informed consent form including the study purpose, methods, extent, risks, benefits, and alternatives. 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 informed consent. All participants will receive a copy of their informed consent and HIPAA forms for their records. The informed consent process will take place in a private room in the Head and Neck Cancer Clinic at each participating site. Only the study participant will provide informed consent. Subjects will be allowed up to one week to decide whether to participate in the study. The signed copy of the informed consent document will be stored in the study binder in each patient's section.

Confidentiality. Protecting the confidentiality of data is essential in any research endeavor but is particularly important in a study that gathers information about sensitive topics. Measures that will be taken to maximize confidentiality and anonymity include the following: (1) all data will be referred to by identification numbers only and (2) data in digital files will be identified by code numbers only. Additionally, digital audio recordings of the interviews will be coded and maintained in password-protected locations on our secure server. The likelihood that these methods will effectively protect the confidentiality of participants is considered to be extremely high. Based on our experience conducting prior similar studies, it is believed that these procedures will be effective in protecting confidentiality of subjects and minimizing any potential risk from participation. Emphasis on confidentiality will be stressed in all aspects of the study. No information about participation in the study will be divulged without specific and written consent to release this information. The only exception would be mandated reporting of allegations of child or elder abuse or disclosures of intent to harm self or others. These confidentiality limits will be documented in the written consent form and verbally explained to all participants.

Data Management. Data will be compiled using codes in lieu of personal identifiers. Prior to and during the study, development of – and security oversight for – the electronic database for this study will be performed by study personnel using REDCap, a secure, web-based, MUSC Information Technology and Institutional Review Board-approved application to support data capture. The application will provide: (1) an intuitive interface for data entry (with data validation); (2) audit trails for tracking data manipulation and export procedures; (3) automated export procedures for seamless data downloads to common statistical packages; (4) procedures for importing data from external sources; and (5) advanced features, such as branching logic and calculated fields. Finally, only de-identified information will be entered into the REDCap electronic database. Thus, no protected health information (PHI) will be entered into the database. The data entry management system will be accessed and housed at MUSC. Although no PHI will be entered into the database, data system security will be ensured by implementing multiple layered firewalls and a network intrusion prevention system for identifying and blocking malicious network activity in real time. An electronic study log linking patient names with study ID numbers will be kept on a secure service at MUSC and access to this log will be limited to only key study personnel.

Responding to Suicidal Ideation Endorsed During Study Interventions. One situation in which study personnel might have to evaluate whether they have a legal or ethical responsibility to break

confidentiality is when there is the potential of danger of the participant to her/himself or to another person. For participants enrolled in the BRIGHT arm, the study interventions will be delivered by a licensed clinical psychologist at each site. Each psychologist is familiar with standard of care and best practices for the assessment and management of suicidal ideation during tele-CBT, which are described in detail in the BRIGHT Therapy Manual. During each BRIGHT session, the psychologist will establish the patient's physical location, nearest emergency medical service provider, and emergency contact information to ensure that the team can intervene if needed. A determination about the appropriateness of the participant for home-based tele-mental health care will be made including the adequacy of infrastructure and technology. Participants will be instructed of legal requirement break confidentiality to notify emergency services for a welfare check should there be concern for the participant or others safety and the participant cannot be properly evaluated by the clinical psychology team (e.g., lost contact with patient and patient cannot be reached again). During sessions, monitoring of risk will occur during treatment (symptom levels, self-harm ideation, intention to harm others, changes in setting/patient situation) as described in the DSMP. If suicidality is endorsed, staff will assess risk, including frequency, lethal means, intent, behavior, and plans. If risk is moderate to low (e.g., no intent or plan), the psychologist and patient will establish a safety plan, including identifying warning signs and internal coping strategies, having the patient or others remove lethal means (e.g., firearms, medication), activating social support, and accessing professional services. Each site will follow its own procedures for sharing regional, and/or national hotlines (e.g., National Suicide Prevention Lifeline = call or text 988). MUSC and Henry Ford also provide local call options (MUSC = 843-792-212, Henry Ford = 314-916-2600 at Henry Ford), while Washington University only uses national hotlines. If risk is deemed to be imminent, the psychologist will call emergency services for immediate psychiatric assessment.

Similar procedures will be followed for the AC arm with modifications for the delivery of AC by the licensed clinical interventionist (e.g., nurse, advanced practice provider) instead of a psychologist. The clinical interventionist will receive standard training in best practices for the assessment and management of suicidal ideation during tele-medicine visits, which are described in detail in the SOP for AC. During each AC session, the clinical interventionist will establish the patient's physical location, nearest emergency medical service provider, and emergency contact information to ensure that the team can intervene if needed. A determination about the appropriateness of the participant for home-based tele-mental health care will be made including the adequacy of infrastructure and technology. Participants will be instructed of legal requirement break confidentiality to notify emergency services for a welfare check should there be concern for the participant or others safety and the participant cannot be properly evaluated by the clinical psychology team (e.g., lost contact with patient and patient cannot be reached again). During sessions, monitoring of risk will occur during treatment (symptom levels, self-harm ideation, intention to harm others, changes in setting/patient situation) as described in the DSMP. If suicidality is endorsed, the clinical interventionists will assess risk, including frequency, lethal means, intent, behavior, and plans. Then, the clinical interventionist will immediately engage the study psychologist at each site to assess risk. If that psychologist is not available, the clinical interventionist will contact the on-call psychologist at each site (who is available 24 hours a day). If risk is moderate to low (e.g., no intent or plan), the psychologist and patient will establish a safety plan, including identifying warning signs and internal coping strategies, having the patient or others remove lethal means (e.g., firearms, medication), activating social support, and accessing professional services. Local, regional, and/or national hotlines will be shared, as is done in standard practice at each site (e.g., National Suicide Prevention Lifeline = call or text 988). MUSC and Henry Ford also provide local call options (MUSC = 843-792-212, Henry Ford = 314-916-2600 at Henry Ford), while Washington University only uses national hotlines. If risk is deemed to be imminent, the licensed clinical interventionist will call emergency services for immediate psychiatric assessment.

Responding to Suicidal Ideation Endorsed During Study Assessments. One of the study assessments, the Beck Scale for Suicidal Ideation, specifically assesses suicidal ideation. Therefore, we have developed a detailed protocol, outlined below, to address endorsements of this item. We have established procedures to automate a "red flag" process within REDCap anytime (in real time) a participant endorses positive values for these questions. This red flag indicator will be checked daily and met with appropriate response from our clinical team. This approach has been utilized in multiple IRB approved trials led by our team and other close collaborators at MUSC. The psychologist at each site will conduct a follow up risk assessment, safety planning, and initiation of emergency services consistent with the procedures described above. For example, with low- to moderate-risk participants, we will establish a collaborative safety plan and provide local, regional, and/or national hotlines with follow-up scheduled as needed; and for participants at imminent risk, the supervisor will call emergency services and remain on the phone with the participant until emergency services arrives, and the study team will follow up with the participant within 72 hours to ensure their continued safety. In the event that a member of our clinical team contacts the participant, the participant expresses an imminent likelihood of harming oneself, and the connection is lost, the psychologist will contact emergency services and will provide emergency services with the participant's contact information and physical location. In the event that the participant is not in imminent danger, the psychologists will provide referrals for local mental health resources and/or instruction to go to a local Emergency Department or call 9-1-1 should suicidal ideation worsen. We will suggest that the participant seek treatment and then will follow up with the participant by phone one week later.

Responding to Physical/Emotional Distress. Measures to protect against study-related psychological and emotional distress (without suicidal/homicidal ideation) during the study intervention or follow up assessments 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 BID). 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.

Participants in either study condition who do NOT have current suicidal or homicidal ideation but nevertheless appear to be experiencing a high level of distress during the study will be asked if they would like to talk to one of site-Pis or associated licensed clinical psychologists. In these instances, the site PI or one of the study psychologists will contact the participant within 24 hours to assess the nature and urgency of the distress, determine the need for clinical intervention beyond any treatment that they may already be receiving, and arrange appropriate mental health referral. In the event that one of the clinical psychologists participating in the trial is not available, a licensed psychologist who works at the relevant site (MUSC, Washington University School of Medicine [WUSM], or Henry Ford Health [HFH]) will be contacted instead. Immediate backup and support will be available. As part of our initial training of the program coordinator at each site, we will work closely with the HFH and WUSM teams to identify local mental health and crisis intervention resources that can be used by Drs. Chang or Pipkorn for referrals should a patient express significant distress in the context of the post-baseline assessment. In rare cases where a mental health referral is needed, the investigator will re-contact the participant

within one week of the referral to determine whether additional resources are needed or if assistance is needed in navigating the referral.

Overall assessment of risks and benefits. 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. Results from the RCT may provide rigorous evidence supporting BRIGHT as the first evidence-based strategy to manage BID among HNC survivors. Such a result would represent a paradigm shift in management of the disorder, help develop new standards of clinical care, and improve psychosocial morbidity and QOL for HNC survivors. Theory-driven mechanism of change data may also help identify specific therapeutic elements to optimize the effectiveness of CBT for BID as well as advance our understanding of the underlying theory of CBT. Furthermore, data from this study will inform the development of a type I hybrid effectiveness-implementation trial evaluating BRIGHT as a new standard of clinical care in a national sample of HNC survivors with BID from diverse cancer care settings.

3 OBJECTIVES AND ENDPOINTS

Table 5. Study Objectives and Endpoints

OBJECTIVES	ENDPOINTS
Primary	
To evaluate the efficacy of BRIGHT compared with AC on HNC-related BID as measured by change from baseline in the IMAGE-HN score.	Change in the IMAGE-HN score from baseline to 6-months follow-up[a]
Secondary	
To evaluate the clinical response rate of BRIGHT compared with AC on HNC-related BID as measured by proportion of patients with a clinically meaningful change from baseline in the IMAGE-HN score.	Proportion of patients with a decrease in the IMAGE-HN score of ≥ 9 points from baseline
To further evaluate the short and longer-term efficacy of BRIGHT compared with AC on HNC-related BID as measured by change from baseline in the IMAGE-HN score.	Change in the IMAGE-HN score from baseline to 2-, 3-, and 9-month follow-up
To evaluate the efficacy of BRIGHT compared with AC on psychological and social well-being as measured by change from baseline in the Shame and Stigma Scale in HNC, PROMIS SF v1.0-Depression 8a, PROMIS SF v1.0-Anxiety 8a, Beck Scale for Suicidal Ideation, and PROMIS SF v2.0-Ability to Participate in Social Activities-8a scores.	Change in the Shame and Stigma in HNC score from baseline to 3-, 6-, and 9-month follow-up
	Change in the PROMIS SF v1.0-Depression 8a score from baseline to 3-, 6-, and 9-month follow-up
	Change in the PROMIS SF v1.0-Anxiety 8a score from baseline to 3-, 6-, and 9-month follow-up
	Change in the Beck Scale for Suicidal Ideation score from baseline to 3-, 6-, and 9-month follow-up
	Change in the PROMIS SF v2.0-Ability to Participate in Social Activities 8a score from baseline to 3-, 6-, and 9-month follow-up
To evaluate the efficacy of BRIGHT compared with AC on QOL as measured by change from baseline in the EORTC QLQ-HN35 score.	Change in the EORTC QLQ-HN35 Trouble with Social Eating and Trouble with Social Contract subscale scores from baseline to 3-, 6-, and 9-month follow-up

Table 5. Study Objectives and Endpoints	
OBJECTIVES	ENDPOINTS
To examine the mechanism of change underlying BRIGHT for HNC-related BID as measured by change from baseline in the Body Image Coping Strategies Inventory (BICSI) subscale scores and Automatic Thoughts Questionnaire scores.	Change in the BICSI Avoidance subscale score from baseline to 2-, 3-, and 6-month follow-up
	Change in the BICSI Positive Rational Acceptance subscale score from baseline to 2-, 3-, and 6-month follow-up
	Change in the BICSI Appearance Fixing subscale score from baseline to 2-, 3-, and 6-month follow-up
	Change in the Automatic Thoughts Questionnaire score from baseline to 2-, 3-, and 6-month follow-up
[a]: All follow-up assessments are measured as time since randomization	
Abbreviations: **AC:** Attention Control; **AE:** Adverse Event; **BICSI:** Body Image Coping Strategies Inventory; **BRIGHT:** Building a Renewed ImaGe after Head & neck cancer Treatment; **EORTC:** European Organisation for Research and Treatment of Cancer; **IMAGE-HN:** Inventory to Measure and Assess imaGe disturbancE-Head & Neck; **PROMIS:** Patient-Reported Outcome Measurement Inventory System; **WAI-SR:** Working Alliance Inventory-Short Revised	

4 STUDY DESIGN

4.1 OVERALL DESIGN

We will perform a multisite RCT comparing BRIGHT with AC to test our hypothesis that BRIGHT reduces BID among HNC survivors as measured by change from baseline in IMAGE-HN score (primary objective). In this multisite, parallel-group RCT, patients from MUSC, WUSM, and HFH 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 stratified permuted block randomization design with randomly selected block sizes of 4 or 6. Randomization will be stratified by site (MUSC, HFH, WUSM) and free flap reconstruction (yes/no) to minimize variability in practices or patient characteristics between sites. Randomization will occur at the individual patient level.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

We considered alternative study designs such as comparison with usual care. Usual care for HNC survivors with BID is educational material provided by HNC providers during routine survivorship visits.[7] Comparison with AC is a strength of our approach because AC controls for professional attention (i.e., ensures that findings are not driven by simply interacting with an empathic interventionist), common factors,[26] dose, and delivery method while not providing the active, behavior change mechanism in BRIGHT.

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 psychosocial care.[63] For patients with HNC, travel burden (due to the regionalization of HNC care[64,65]) is a critical barrier to mental health care and contributes to excess morbidity and mortality.[66,67] 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 psychosocial interventions to HNC survivors are needed.[68,69] Telemedicine is a promising solution because it decreases travel burden[70], increases access to care[71], and provides effective behavioral health interventions[72] (including CBT[63,73]). 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.[16]

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

The number, frequency, and timing of BRIGHT sessions was justified based on our formative work. Stakeholder feedback from HNC survivors and clinicians helped define BRIGHT's timing (early post-treatment), setting (one-on-one therapy), duration (limited number of sessions), and delivery method. The number, frequency, and timing of BRIGHT sessions was then evaluated in our single-arm clinical trial (NCT03518671) (**Table 2**)[16] and single-site pilot RCT (NCT03831100). Patients in BRIGHT rated the timing of the intervention relative to HNC treatment highly (all mean ≥ 4/5/5) (**Table 3**).

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-, 3-, and 6-month post-treatment assessments. The end of the study is defined as completion of the 6-month post-treatment assessment shown in the SoA, **Section 1.2**.

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 on the day of informed consent
2. History of pathologically confirmed squamous cell carcinoma (or histologic variant) of the 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. Completion of oncologic treatment within 12 months of study enrollment (but no sooner than 6 weeks post-treatment completion)
    a. Patients who complete definitive HNC-directed therapy (e.g., surgery or radiation therapy) but are on an adjuvant immunotherapy trial are considered eligible
5. Cancer-free at the time of accrual
    a. Patients with known indolent malignancies (e.g., non-melanoma skin cancer, low risk thyroid cancer, untreated prostate cancer, etc.) would not exclude a patient from the study
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. IMAGE-HN score ≥ 22

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 read English
2. Pre-existing, ongoing psychotherapy services for any disorder and the participant is not willing to discontinue the prior therapy for the duration of the proposed trial
3. Initiation or adjustment (≤ 3 months of baseline) of psychotropic medication
4. Severe mental illness that would prevent trial participation

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 randomized or entered in the study due to not meeting 1 or more eligibility criteria. Individuals who do not meet the criteria for participation in this trial (screen failure) because of meeting one or more exclusion criteria may be rescreened if the investigator believes that there has been a change in eligibility status. Patients who re-screen must re-consent.

5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

5.5.1 ANTICIPATED SCREENING AND ACCRUAL TARGETS

To achieve our target sample of N = 180 evaluable patients with an expected attrition rate of 20%, we plan to enroll 226 patients. Patients will be accrued from three sites: MUSC, WUSM, and HFH. The planned accrual stratified by gender, race, and ethnicity is shown in **Table 6.** We will recruit by age and sex in proportion to the population; this approach resulted in a diverse sample in our pilot RCT. 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 and (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 in this patient population. The study sites where clinic-based recruitment and enrollment will occur (MUSC, WUSM, HFHS) all have appropriate facilities to accommodate individuals in the included age range.

Table 6. Planned Recruitment by Race, Ethnicity, and Gender

Racial Categories	Ethnic Categories				
	Not Hispanic or Latino		Hispanic or Latino		Total
	Female	Male	Female	Male	
Asian	3	3	0	0	3
Black	22	23	0	0	45
White	60	60	5	4	129
≥ 1 Race	0	0	0	0	0
Total	85	86	5	4	180

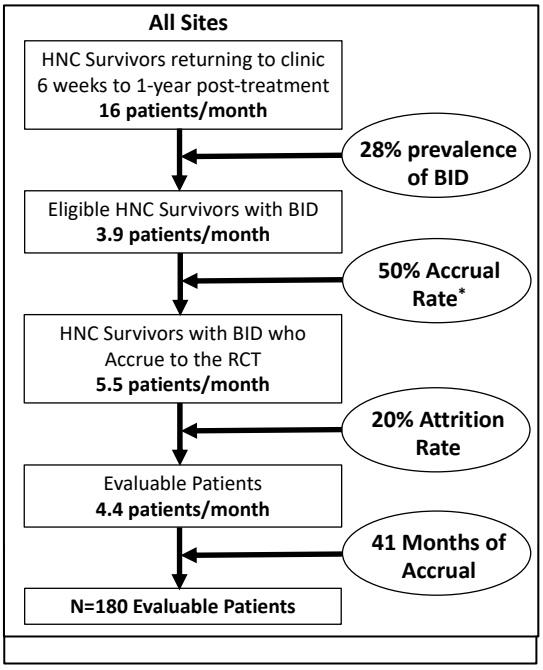
There are no inclusion or exclusion criteria based on sex. The planned distribution of subjects by sex in the clinical trial is 50% female and 50% male. The distribution is expected to reflect the demographics of our target population (HNC survivors with BID following surgery) based on our prior studies at each of

the three sites. None of the three sites have experienced any difficulty in achieving equality in representation by sex in prior studies in this patient population.

Patients of all races and ethnicities will be recruited for the study. The population distribution of subjects by self-identified race in the catchment areas for the three sites is 77% white, 16% Black and 7% other. However, significant Black/White racial disparities in outcomes exist in HNC; it is thus critical that we enroll a racially diverse population to ensure the external validity of trial findings. Therefore, we will stratify accrual by race (Black vs White/other) and oversample Black patients (25%) relative to their frequency in our population (16%). The PI and research team will leverage their experience and strong track record of recruiting and engaging underserved and racial minorities in their HNC research. The planned distribution of subjects by self-identified ethnicity in the trial is 95% non-Hispanic and 5% Hispanic. The rationale for the selection of ethnic proportions in the proposed trial is that prior studies have demonstrated no association between ethnicity and BID among HNC survivors.

5.5.2 ANTICIPATED ACCRUAL RATE AND ACCRUAL FEASIBILITY

Targeting an attrition rate = 20%, we propose to enroll 226 patients to achieve a final sample size of N = 180 evaluable patients. In the pilot RCT of BRIGHT at MUSC, we accrued 54 eligible patients in 17 months (3.2 patients/month); 87% (54/62) of eligible patients accrued to the study. Below we outline our assumptions to demonstrate the feasibility of recruitment and retention for the proposed multisite RCT (**Figure 7**). Clinical volumes are similar at MUSC, HFH, and WUSM and thus we present the data in its aggregate across all three sites.



We estimate n = 16 HNC survivors returning to clinic/month based on (1) registry data from each cancer center and (2) recruitment for HNC survivors with BID at prior studies at MUSC, HFH, and WUSM. We estimate the prevalence of BID among HNC survivors at 28% based on (1) our prior cohort studies of HNC survivors at MUSC, HFH, and WUSM[4] and (2) screening for our pilot RCT of BRIGHT at MUSC. We target an accrual rate of 50% for the proposed multisite RCT. This is a highly conservative estimate since we accrued 87% of eligible HNC survivors with BID to the pilot RCT of BRIGHT. At the targeted conservative accrual rate of 5.5 patients/month, we would accrue N = 226 patients in 41 months. We estimate an attrition rate of 20% based on our pilot RCT of BRIGHT and other trials we have conducted among HNC survivors.

5.5.3 PLANNED SCREENING AND RECRUITMENT STRATEGIES

The multidisciplinary HNC team (surgical, radiation, and medical oncologists, and advanced practice providers for each specialty) actively participated in the recruitment and retention of HNC survivors with BID in prior studies. The HNC team at each site is thus already aware of our ongoing studies and clinical trials in this area. As we prepare to recruit for the proposed RCT, the site-PI will introduce the new clinical trial concept to the HNC team at their weekly multidisciplinary HNC tumor board. The site-PI will also conduct in-person staff trainings about recruitment protocols during the initial planning period and

review sessions as needed throughout the enrollment process. We have developed project recruitment milestones and metrics. We will review progress and troubleshoot recruitment issues if they arise during weekly team-wide study meetings. It is expected that each site-PI, as a clinically active HNC surgeon, will help engage other members of the multidisciplinary HNC team in the recruitment planning efforts.

The program coordinator at each site (MUSC, HFH, WUSM) will screen for potential participants using the electronic health record (EHR) to preview the weekly HNC clinic schedule. EHR-based screening will be supplemented by in-person discussion with the HNC clinical team at each site to optimize identification of potentially eligible patients. Research staff will review clinical documentation for all HNC survivors with an appointment in the HNC clinic to identify patients who meet clinical study inclusion criteria and are scheduled for an appointment. 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 treating physician will approach the potential participant to introduce the research study directly to the patient at the clinic visit. Study information provided by the clinician will not include any language or information that may be perceived as unduly influencing or coercive, or imply that medical care could be influenced by choice to participate or not. If the patient is interested in the research study, then he/she will contact the research team for more information.

If the patient is interested in participating in the research study, the program coordinator will discuss participation in the trial at that clinical encounter. Because IMAGE-HN is not used in clinic as standard of care at each site, a waiver of documentation of the informed consent process will be utilized to allow for IMAGE-HN to be used as a screening tool for the trial. The potential participant will complete the IMAGE-HN to determine trial eligibility; those with an IMAGE-HN score <22 do not have clinically significant HNC-related BID and thus are not eligible. At this in-person clinic visit the program coordinator will confirm the rest of the inclusion/exclusion criteria that could not be obtained in the EHR.

Each site (MUSC, HFH, WUSM) will use a clinic-based screening and recruitment approach that we optimized in our prior studies.[4,16,27,40] Recruitment for the study will occur using the standard operating procedures (SOPs) that we optimized during our single-arm and pilot RCTs of BRIGHT at MUSC. These SOPs will be adapted and optimized for clinic workflow at HFH and WUSM. The recruitment protocols have been optimized based on our experiences in prior studies to address logistical issues related to coordination of clinic-based screening and enrollment. Our experience recruiting for BRIGHT also demonstrated that the active clinical practice of the site-PI and his clinical relationship with all members of the multidisciplinary HNC team are key factors in maximizing recruitment. Recruitment at each site will be handled by the project coordinator and study team at that site.

5.5.4 STRATEGIES TO ENHNACE RETENTION

We expect to continue the high rate of retention that we demonstrated in our single-arm and pilot RCT through the following five 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/AC session helped ensure low rates of missed sessions and high rates of retention. Second,

BRIGHT was designed using a patient-centered 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 and AC differ, the timing and delivery method are the same in both arms of the trial and will thus likely facilitate retention in the AC arm 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 studies 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. Fifth, we strive to compensate 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 assessments.

5.5.5 RETENTION FEASIBILITY

Our prior studies demonstrate our strong track record of retention. In our pilot RCT of BRIGHT, 20% of accrued patients (11/54) went off study: n = 7 (13%) went off study per protocol due to the development of HNC recurrence or second non-HNC malignancy; n = 3 (7%) withdrew due to intercurrent physical demands, and n = 1 (2%) was enrolled erroneously. We are encouraged by the very low rate of withdrawal (7%) and the finding that no evaluable patients were lost to follow-up. The rate of recurrence or second primary non-HNC malignancy was significantly higher than expected based on population data and is likely an aberrant finding in a small sample. We do not expect the rate of patients going off protocol due to recurrent HNC or second non-HNC primary malignancies to stay this high in the larger sample for the proposed multisite RCT. In our single-arm study of BRIGHT, retention was 90% (9/10 participants).[16] The 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.

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 a manualized theory-based tele-CBT intervention consisting of 6 weekly 60-minute sessions. BRIGHT will be delivered one-on-one by a licensed clinical psychologist at each site (MUSC, HFH, WUSM)

via standard video tele-CBT platform. BRIGHT is situated within a cognitive psychology perspective[19] of BID and conceptualizes HNC-related BID according to Folkman's transactional theory of stress and coping.[17,24,46,55] **Table 7** shows the psychotherapeutic techniques utilized in BRIGHT to address key theorized targets.

Table 7. BRIGHT Psychotherapeutic Techniques and Objectives

Technique	Session Objectives
Psycho-education	-Understand the cognitive model of body image and how HNC survivors are affected by BID
Self-Monitoring	-Learn how thoughts, feelings, and behaviors about body image are related -Begin to self-monitor situations that contribute to BID
Cognitive Restructuring	-Identify unhelpful automatic HNC body image schemas -Challenge unhelpful automatic HNC body image thoughts and substitute more balanced thoughts
Body Image Coping Strategies	-Identify body image avoidance behaviors and recognize how they increase long-term BID -Develop an action plan for situations that are being avoided
Relapse Prevention	-Reflect on progress made during BRIGHT -Set goals aligned with personal values to prevent relapse

Psychologists deliver BRIGHT according to the BRIGHT Manual, which outlines the underlying theoretical basis of BRIGHT as well as the topics, objectives, psychotherapeutic techniques, and content for each session. Patients receive the BRIGHT Patient Workbook, which contains objectives, educational materials, exercises, and homework for each week. The BRIGHT materials were developed with engagement from HNC survivors to ensure that the content was language and literacy-level appropriate and refined with HNC survivors from our single-arm trial and pilot RCT to optimize relevance, clarity, and readability.

Psychologists at each site (MUSC, HFH, WUSM) have experience delivering video tele-mental health care to patients with HNC. The HIPAA-compliant and institutionally-approved video telemedicine platform at each site uses face to face communication and includes a within-video text feature for patients with challenges speaking due to surgical removal of the voice box or tongue. Although the COVID-19 pandemic rapidly accelerated the uptake of telemedicine for HNC survivorship care[77,78] and CBT,[79,80] the potential for a digital divide remains.[81] To enhance equity and minimize the digital divide, we will provide patients with a study-issued, cellular-enabled iPad if needed, show patients how to use the iPad and telemedicine platform, and provide patients with a pictorial instructional booklet for home reference. Each iPad is locked to prevent downloading of additional applications, pre-loaded with a HIPAA-compliant video teleconference platform, and has cellular service with > 97% coverage for each state.[82] Patients receive a pre-addressed, stamped, padded mailer to return the iPad. We successfully delivered BRIGHT using this approach in our single-arm trial[16] and pilot RCT.

6.1.1.2 AC

Following best practices for choosing control groups within behavior change RCTs,[83,84] we designed AC to control for professional attention (i.e., ensuring that findings are not driven by simply interacting with an empathic interventionist), common factors,[26] dose, and delivery method while not providing the active, behavior change mechanism in BRIGHT. AC is a manualized tele-supportive care intervention delivered by licensed HNC clinical staff (e.g., advanced practice provider) at each site (MUSC, HFH, WUSM) that addresses non-body image aspects of HNC survivorship. The AC manual provides educational content (**Table 8**) and directs the interventionist to provide empathic comments but contains no psychotherapeutic techniques. The manual also outlines the hypothesized behavior change mechanisms in BRIGHT that should not be addressed by AC and provides strategies for the interventionist to re-direct the conversation if BID arises. Identical to BRIGHT, AC consists of 6 weekly 60-minute sessions delivered by a trained empathic interventionist via standard video-telemedicine

(with iPad provision if necessary). AC is an adaptation of the control intervention used in our pilot RCT that we modified for manualized delivery by an interventionist. We pre-tested the interventionist-delivered AC with HNC survivors and then refined it based on their feedback to optimize its feasibility, credibility, and relevance.

Table 8. Attention Control Topics and Objectives

#	Topic	Objectives
1	Survivorship Intro	Understand the new normal of HNC survivorship
2	HNC Physical Treatment Toxicity	Learn ways to manage physical changes including radiation side effects, dysphagia, and lymphedema
3	Psychosocial Effects of HNC	Normalize post-treatment psychosocial changes including anxiety and depression
4	Health Maintenance	Develop strategies for a healthy diet and exercise; address nutritional challenges for HNC survivors
5	Financial Toxicity & Return-to-Work	Discuss strategies to get back to work and manage finances following HNC treatment
6	Fear of Cancer Recurrence	Learn ways to manage fear of cancer recurrence

6.1.2 ADMINISTRATION AND/OR DOSING

BRIGHT and AC will be delivered using the same telemedicine delivery platform at each site (MUSC, HFH, WUSM). The Health Insurance Portability and Accountability Act (HIPAA)-compliant and institutionally-approved video telemedicine platform at each site uses face to face communication and includes a within-video text feature for patients with challenges speaking due to surgical removal of the voice box or tongue. Although the COVID-19 pandemic rapidly accelerated the uptake of telemedicine for HNC survivorship care[77,78] and CBT,[79,80] the potential for a digital divide remains.[81] To enhance equity and minimize the digital divide, we will provide patients with a study-issued, cellular-enabled iPad if needed, show patients how to use the iPad and telemedicine platform, and provide patients with a pictorial instructional booklet for home reference. Each iPad is locked to prevent downloading of additional applications, pre-loaded with a HIPAA-compliant and institutionally-approved video teleconference platform, and has cellular service with > 97% coverage for each state.[82] Patients receive a pre-addressed, stamped, padded mailer to return the iPad. We successfully delivered BRIGHT using this approach in our single-arm trial[16] and pilot RCT.

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 standard of care video telemedicine platform. The BRIGHT intervention consists of 6 sessions of weekly, 60-minute, tablet-based, manualized individual video tele-CBT (see **Section 1.3, Schedule of Activities**). BRIGHT will be delivered by licensed clinical psychologists at each site with experience delivering manualized CBT and working with cancer survivors. The use of multiple psychologists to deliver BRIGHT will enhance rigor and external validity and minimize confounding between the experimental intervention and interventionist. The relevant parameters when considering the delivery of BRIGHT include the number, frequency, and duration of telemedicine 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 will be delivered in one-on-one, face-to-face sessions between the clinical provider and participant using a standard of care video telemedicine platform (see **Section 1.3, Schedule of Activities**). The relevant parameters when considering the delivery of AC include the number, frequency, and duration

of video telemedicine sessions to ensure that it is appropriately matched to BRIGHT. AC controls for professional attention (i.e., ensuring that findings are not driven by simply interacting with an empathic interventionist), common factors,[26] dose, and delivery method while not providing the active, behavior change mechanism in BRIGHT. 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

6.2.1.1 BRIGHT

BRIGHT will be delivered by licensed clinical psychologists at each site (MUSC, HFH, WUSM) with experience delivering manualized CBT and working with cancer survivors. Dr. Maurer, the psychologist who helped develop BRIGHT with Dr. Graboyes, will train the psychologists at each site. BRIGHT training will occur virtually for 12 hours over 3 days. Training will include (1) background readings and a guided discussion about HNC-related BID, (2) comprehensive and interactive orientation to the BRIGHT Therapy Manual and Patient Workbook, (3) review of previously recorded BRIGHT sessions, (4) simulated BRIGHT delivery via roleplay with mock participants, and (5) discussion of study protocol and standard operating procedures (SOPs). Following training, Dr. Maurer will meet with the interventionists virtually once/month to discuss challenges delivering BRIGHT.

6.2.1.2 AC

AC will be delivered by licensed HNC clinical staff at each site (MUSC, HFH, WUSM) with experience working with HNC survivors. A HNC survivorship Physician Assistant at MUSC will work with Dr. Graboyes to train the AC Interventionists to deliver AC using the methods described above (but adapted for AC).

6.2.2 INTERVENTION FIDELITY

We will ensure the consistent delivery of study interventions (BRIGHT, AC) via the following mechanisms. First, tele-sessions in both groups will be recorded. The trained PC will review randomly selected sessions (17%) to monitor for therapeutic drift[85] and assess fidelity quantitatively using a modified version of the BRIGHT Fidelity and Competence Scale.[86] Second, at the conclusion of each session, the interventionist will complete the electronic case report form (eCRF) for fidelity monitoring which assesses session completion, duration, content delivered, and delivery mode. For AC, fidelity monitoring will also include assessments of negative fidelity to ensure that BID is not discussed. The accuracy of fidelity self-reporting for the video-recorded sessions is enhanced through the bogus pipeline.[87] Third, the specific duties necessary to ensure consistent and optimal delivery of the interventions (BRIGHT, AC) are detailed in the respective manuals, thereby minimizing therapeutic drift.[85] If insufficient fidelity to the manual is identified, the interventionist will be remediated until competency is demonstrated.

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. Following provision of written informed consent and completion of baseline study assessments, patients will be randomized 1:1 to BRIGHT or AC using a stratified permuted block

randomization design with randomly selected block sizes of 4 or 6 to avoid deterministic treatment allocation. Randomization will be stratified by site (MUSC, HFH, WUSM) and free flap reconstruction (yes/no) to minimize variability in practices or patient characteristics between sites. The random allocation sequence will be generated by the lead study biostatistician using a computer-generated algorithm. The program coordinator will implement the random allocation sequence using the REDCap randomization feature to conceal the sequence until intervention assignment. Randomization errors will be handled as per ITT analyses for the efficacy population.

Study investigators will be blinded to allocation. Outcome assessors are not blinded to allocation, but all study assessments are patient-reported outcomes and thus unlikely to be biased by outcome assessors knowing study allocation. Staff delivering BRIGHT/AC cannot be blinded due to face-to-face intervention delivery. Patients are not blinded but they also are not instructed whether BRIGHT or AC is the active intervention.

6.4 STUDY INTERVENTION ADHERENCE

Adherence of subjects to BRIGHT/AC 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 (for BRIGHT); (4) interventionist rating of patient engagement and material comprehension. Attendance at all study visits is mandatory to remain an active participant. Adherence information will be assessed by the interventionist and documented in the eCRF after each study visit.

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. 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

The date and reason for participant discontinuation or withdrawal from the study will be recorded in the eCRF.

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 5 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 using a variety of contact modalities (e.g., telephone call, email, text message, communication through the EHR). 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

Each site (MUSC, HFH, WUSM) will be responsible for collecting study assessment data as described below and entering it into the REDCap eCRFs. There will be a single central REDCap developed and maintained at MUSC.

8.1 SCREENING PROCEDURES

The program coordinator at each site (MUSC, HFH, WUSM) will screen for potential participants using the EHR to preview the weekly head and neck oncology clinic schedule at each site. EHR-based screening will be supplemented by in-person collaboration with the head and neck clinical team at each site. Research staff will review clinical documentation for all new or returning patients with an appointment in the head and neck clinic to identify patients who meet clinical study inclusion criteria and are scheduled for an appointment. 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 within the head and neck clinic to discuss participation in the trial. All screening information and criteria necessary to establish trial eligibility

other than the IMAGE-HN score are available in the HER but will be confirmed with the patient and treating clinician

After a patient who is potentially eligible for the study is identified, the patient will be contacted at the previously identified clinic visit to discuss participation in the study as described below. The head and neck oncology clinician 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 program 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 the IMAGE-HN as a screening assessment to identify patients with clinically significant HNC-related BID; those with score $\geq$ 22 will be eligible for the study.

Once a subject has signed the informed consent form (ICF), an identification number will be assigned to him/her and the study related screening procedures will start. A subject will be randomized into the study after he/she has signed the ICF and all eligibility criteria have been met.

8.2 BASELINE ASSESSMENTS

8.2.1 DEMOGRAPHIC

Demographic information is gathered as patient self-report in the eCRF. Demographic characteristics include sex, age, race, ethnicity, marital status, insurance, educational attainment, employment, and history of medication or counseling for mental health disorders.

8.2.2 CLINICAL AND ONCOLOGIC

Clinical and oncologic characteristics are assessed using clinical documentation within the EHR unless otherwise indicated.

Baseline oncologic characteristics include history of mental health diagnoses, concomitant antidepressant or anxiolytic usage, head and neck tumor subsite, tumor histology, p16/human papillomavirus (HPV) tumor status, date of treatment completion, head and neck cancer treatment modalities, type of ablative surgery, type of surgical reconstruction, American Joint Committee on Cancer (AJCC) 8th edition pathologic TNM Class, AJCC 8th edition overall pathologic stage grouping.

8.3 ENDPOINT AND OTHER NON-SAFETY ASSESSMENTS

Sites are encouraged to administer patient-reported outcome measures (PROMs) using an electronic device/tablet. If that is not feasible, administration of PROMs using a paper-based format is also acceptable. Sites are encouraged to align PROS 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, text message, or email at the program 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.

8.3.1 EFFICACY

IMAGE-HN. The IMAGE-HN is a 24-item, validated, PROM of HNC-related BID.[27] Items are rated on a 5-point Likert scale from 'Never' (0) to 'Always' (4). The total global score is calculated by summing item responses across 21 items (all items except 3, 4, and 19). The total IMAGE-HN score on the global

domain (21 questions) ranges from 0-84; higher scores indicate worse HNC-related BID. An IMAGE-HN score of ≥ 22[4] indicates clinically-significant HNC-related BID and a change in IMAGE-HN score of ≥ 9 points is clinically meaningful.[88]

Shame and Stigma Scale in HNC. The Shame and Stigma Scale in HNC 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.[31] Items are rated on a 5-point Likert scale from 'Never' (0) to 'All the time' (4). The total score is calculated by summing the individual responses (except for 4 questions which are reverse scored). Shame and Stigma Scale in HNC scores range from 0-80; higher scores reflect worse HNC-related shame and stigma.

PROMIS SF v1.0- Depression 8a. The PROMIS SF v1.0-Depression 8a is an 8-item validated measure developed by the NIH to assess patient-reported negative mood, views of self, and decreased positive affect and engagement.[89] Responses rate the strength of agreement with statements about depressive symptoms using a scale that ranges from 1-5. The total raw score is calculated by summing the individual responses. The PROMIS SF v1.0-Depression 8a raw score ranges from 8-40; a higher score reflects more severe depressive symptoms. The PROMIS SF v1.0-Depression 8a total raw score is translated into a T-score for each participant according to the PROMIS Scoring manual. The T-score provides a standardized score with a mean of 50 and a standard deviation of 10.

PROMIS SF v1.0-Anxiety 8a. The PROMIS SF v1.0-Anxiety 8a is an 8-item, validated, developed by the NIH to assess patient-reported fear, worry, and hyperarousal.[89] Responses rate the strength of agreement with statements about anxiety symptoms using a scale that ranges from 1-5. The total raw score is calculated by summing the individual responses. The PROMIS SF v1.0-Anxiety 8a raw score ranges from 8-40; a higher score reflects more severe anxiety symptoms. The PROMIS SF v1.0-Anxiety 8a total raw score is translated into a T-score for each participant according to the PROMIS Scoring manual. The T-score provides a standardized score with a mean of 50 and a standard deviation of 10.

Beck Scale for Suicidal Ideation. The Beck Scale for Suicidal Ideation is a 21-item, validated, patient-self report rating scale to rate the severity of a patient's suicidal thoughts and plans.[90] Each item consists of three options graded according to suicidal intensity from 0 to 2. The ratings for the first 19 items are summed to yield a total score, which ranges from 0 to 38. Higher scores represent more severe suicidal ideation.[91] A cutoff score of > 2 is optimal to indicate high/low risk of suicidal ideation.[92]

PROMIS SF v2.0-Ability to Participate in Social Activities 8a. PROMIS SF v2.0-Ability to Participate in Social Activities 8a is an 8-item, validated, unidimensional measure of patient-reported perceptions of participation in social activities.[93,94] Items are scored using a 5-point Likert scale from 'Never' (1) to 'Always' (5). The total raw score is calculated by summing the individual responses. The total raw score ranges from 8-40; a higher score reflects more severe inability to participate in social activities. The total raw score is translated into a T-score for each participant according to the PROMIS Scoring manual. The T-score provides a standardized score with a mean of 50 and a standard deviation of 10.

EORTC QLQ-HN35 Trouble with Social Eating Subscale. The EORTC QLQ-HN35 Trouble with Social Eating Subscale is a 4-item, validated measure of trouble with social eating for patients with HNC.[95] The subscale is composed of QLQ-H&N35 items 19-22. Items are scored using a 4-point Likert scale from 'not at all' (0) to 'very much' (3). The total score is calculated by summing the individual responses. Total subscale scores range from 0-12; higher scores reflect more trouble with social eating.

EORTC QLQ-HN35 Trouble with Social Contact Subscale. The EORTC QLQ-HN35 Trouble with Social Contact Subscale is a 5-item, validated measure of trouble with social contact for patients with HNC.[95] The subscale is composed of QLQ-H&N35 items 18, 25-28. Items are scored using a 4-point Likert scale from 'not at all' (0) to 'very much' (3). The total score is calculated by summing the individual responses. Total subscale scores range from 0-15; higher scores reflect more trouble with social contact.

8.3.2 MECHANISM

Body Image Coping Strategies Inventory. The BICSI is a 29-item, validated measure of the cognitive and behavioral responses to manage threats to body image.[55] 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' (0) to 'Definitely like me' (3). The score for each subscale is calculated by summing the values for the individual questions and thus ranges as follows: Appearance fixing (0-30), Avoidance (0-24), and Positive rational acceptance (0-33). For each subscale, higher scores indicate greater reliance on that type of body image coping strategy.

Automatic Thoughts Questionnaire. The Automatic Thoughts Questionnaire is a 15-item, validated, patient-reported measure of negative automatic thoughts.[96] Items are scored using a 5-point Likert scale (1-5). The total score is calculated by summing the individual responses. Total scores range from 15-75; higher scores reflect more negative automatic thoughts.

Working Alliance Inventory-Short Revised-Therapist. The Working Alliance Inventory Short Revised-Therapist Version is a 10-item, validated, assessment of the strength of alliance (bond, goals, task) between the therapist and client, as rated by the therapist.[76] Items are scored using a 5-point Likert scale from 'Seldom' (1) to 'Always' (5). The total score is calculated by summing the individual responses. The total score ranges from 10-50; higher scores reflect stronger alliance (bond, goal, task) between the therapist and the client as rated by the therapist.

Therapist Empathy Scale. The Therapist Empathy Scale is a 9-item validated measure of therapist empathy as rated by a 3rd party observer.[97] Items are scored using a 7-point Likert scale from 1-7. The total score is calculated by summing the individual responses and thus ranges from 9-63. Higher scores reflect more frequent empathy by the therapist.

Credibility/Expectancy Questionnaire-Expectancy Subscale. The Credibility/Expectancy Questionnaire-Expectancy Subscale is a 3-item, validated assessment of the patient's expectations for improvement with the intervention.[98] Items are scored using a 9-point Likert scale from 1-9. The total score is calculated by summing the individual responses and thus ranges from 3-27. Higher scores reflect greater expectation of improvement from the intervention.

8.3.3 INTERVENTION FIDELITY

BRIGHT Fidelity and Competence Scale. The BRIGHT Fidelity and Competence Scale is a system for rating the fidelity and skill level of therapists delivering BRIGHT that consists of 11 items grouped in 3 subscales: Assessment (1 item), General (4 items), and BRIGHT (6 items). All of the items use a common Likert-type scale from 1-7. For each item, two dimensions are rated using this Likert scale. The first dimension, 'Frequency and Extensiveness', is a 'quantity' or 'fidelity' rating that taps the degree to which

the intervention was present in that session (e.g., whether it occurred and with what intensity). The second dimension, 'Skill Level', is a 'quality' or 'competence' rating that indicates skill with which the therapist delivered the intervention (and is rated only if the intervention occurred within the rated session). 'Frequency and Extensiveness' is rated on a Likert scale of 1-7 (not at all to extensively) with higher scores reflecting greater frequency and extensiveness of the item. 'Skill level' is rated from 1-7 (very poor to excellent) with higher scores reflecting greater skill on each item. The BRIGHT Fidelity and Competence Scale is modeled from the Yale Adherence and Competence Scale (YACS), a validated scale for rating therapist adherence and competence in delivering behavioral treatments for substance use disorders.[86] Details for scoring and interpreting the BRIGHT Fidelity and Competence Scale are provided in its accompanying Rater Manual.

Interventionist Self-Report. The Interventionist Self-Report is a self-report checklist (yes/no) mapped to agenda content for each of the 6 sessions for BRIGHT or AC.

8.3.4 PARTICIPANT ADHERENCE

Adherence will be assessed with the following measures: (1) attendance at intervention visits; (2) duration of study visits; (3) homework completion (for BRIGHT); (4) interventionist rating of patient engagement and material comprehension.

8.4 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.4.1 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 sustained undesirable psychological, social, or emotional reaction that is definitely, probably, or possibly related to the study intervention. AEs include suicide attempt, sustained emotional distress, sustained depression, or other sustained mental health deterioration. This definition of an adverse event follows best practices for recording adverse events during psychological treatments. [99]

8.4.2 DEFINITION OF SERIOUS ADVERSE EVENTS

A serious adverse event (SAE) will be defined as any sustained undesirable psychological or mental health 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.

8.4.3 CLASSIFICATION OF AN ADVERSE EVENT

8.4.3.1 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".

8.4.3.2 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.

8.4.4 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. AEs may be reported by the patient via self-report, noted in the electronic medical record, or reported directly by study personnel.

8.4.5 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 at each site. 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

8.4.6 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.

8.4.7 REPORTING EVENTS TO PARTICIPANTS

N/A

8.4.8 EVENTS OF SPECIAL INTEREST
N/A

8.4.9 REPORTING OF PREGNANCY
N/A

8.5 UNANTICIPATED PROBLEMS

8.5.1 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.

8.5.2 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 National Cancer Institute (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

8.5.3 REPORTING UNANTICIPATED PROBLEMS TO PARTICIPANTS
N/A

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESIS

We hypothesize that, compared with patients randomized to AC, patients randomized to the BRIGHT intervention will have reduced BID as measured by change in the IMAGE-HN score of $\geq$ 9 from baseline to 6-months follow-up. Alternatively, our null hypothesis is that BRIGHT will not improve BID relative to AC, as measured by change in the IMAGE-HN score of < 9 from baseline to 6-months follow-up.

9.2 SAMPLE SIZE DETERMINATION

The primary endpoint for the proposed RCT is the change in the IMAGE-HN score from baseline to 6-month follow-up. Our primary objective is to test the hypothesis that BRIGHT decreases HNC-related BID from baseline to 6-month follow-up (as measured by clinically significant reduction in the IMAGE-HN score) relative to AC. We target a mean difference in IMAGE-HN score reduction of 9 between BRIGHT and AC at 6 months. This targeted difference is (1) clinically important using widely accepted distribution-based methods of patient reported outcome measure interpretation[88] and (2) commensurate with clinically meaningful differences in BID among cancer survivors from other appropriately powered trials.[14,41,100] In our pilot RCT, at 3-months post-intervention (a timepoint similar to 6 month follow-up), BRIGHT improved IMAGE-HN scores from baseline relative to AC (mean model-based difference in change in IMAGE-HN score = -17.1 [90% CI, -25.6 to -8.6] points; P = 0.002). The targeted clinically important difference in IMAGE-HN score reduction of 9 thus appears highly feasible. Determining the sample size for the proposed RCT requires adjusting for the clustering of trial participants within psychologist (BRIGHT arm) or HN clinical staff member (AC arm). We expect the number of clusters in each arm to be 9 with an average of 10 trial participants per cluster. We further estimate an intra-class correlation coefficient (ICC) = 0.05[101,102] and standard deviation = 16 based on similar studies.[41,100] Given these assumptions, a sample size of N = 180 (n = 90/arm) yields 83.7% power to detect the targeted 9-point average reduction in IMAGE-HN scores between the BRIGHT and AC arms with two-sided α = 0.05 (PASS v 08.0.13, Inequality Tests for Two Means in a Cluster-Randomized Design module).

Targeting an attrition rate = 20%, we plan to enroll 226 HNC survivors with BID to achieve our target sample size of N = 180 evaluable patients for the modified intention-to-treat (ITT) analyses of the efficacy population. In our pilot RCT, 20% (11/54) of eligible patients who accrued to the RCT were not evaluable for the primary endpoint: n = 7 (13%) went off study per protocol due to the development of recurrent HNC or a second non-HNC malignancy; and n = 3 (7%) withdrew due to intercurrent physical demands. No patients were lost to follow-up.

9.3 POPULATIONS FOR ANALYSES

The **safety analysis set** (SAS) is composed of all patients enrolled who receive any part of either the BRIGHT or AC intervention. The SAS will be used to conduct all safety analyses. Patients will be analyzed based on the intervention received regardless of the assignment at randomization.

The **6-month IMAGE-HN evaluable set** is composed of all patients enrolled in the trial who have completed the baseline and 6-month follow-up IMAGE-HN survey instrument. Analysis will be performed based on assignment at randomization regardless of the intervention received (modified intent to treat). This analysis set will be used for analysis of the primary endpoint.

Analysis sets for secondary endpoints specific to PROMs at a given follow-up timepoint will be defined as the set of trial participants who have completed both the baseline and the follow-up survey at the specified timepoint. Analysis will be performed based on assignment at randomization regardless of the

intervention received (modified intent to treat). These analysis sets will be used for analysis of the secondary endpoints (**Table 5**).

The **full analysis set (FAS)** is the set of all trial participants who enroll and are eligible for the study. Patients who enroll but subsequently drop out prior to receiving any of the assigned intervention will be replaced. This analysis set will be used for secondary analyses of both the primary endpoint and secondary endpoints.

Per protocol set is composed of all patients enrolled in the trial who have completed 6-weeks of the BRIGHT/AC interventions as described in the protocol. This analysis set will be used for secondary analyses of both the primary endpoint and secondary endpoints.

Details about the analytic plan for each population are described in detail in **Section 9.4**.

9.4 STATISTICAL ANALYSES

A statistical analysis plan (SAP) will be developed prior to database lock. The SAP will detail all planned analyses and analytic methods.

All statistical analyses will be performed using SAS or R packages. Graphical displays (e.g., bar charts, boxplots) and summary statistics (e.g., mean, median, standard deviation, interquartile range) will be used to characterize the data. Two sample t-tests or non-parametric Wilcoxon rank-sum tests will be used to compare continuous measures. Normality and variance homogeneity assumptions will be assessed, with appropriate data transformations as needed. The chi-square test will be used to evaluate associations between discrete variables.

9.4.1 MISSING DATA

The analytic method for the primary endpoint will be generalized estimating equations (GEEs), which requires missing data to be missing completely at random for valid inference. We expect the rate of missing data to small and anticipate GEE analysis to be appropriate. However, if the rate of missing data is significant, we will use linear mixed effect regression (LMER) as our primary analytic approach and GEEs as a secondary approach. A review of the data will be performed prior to database lock to establish overall rates of missingness for the primary endpoint and the SAP updated if needed to reflect any changes in planned analyses.

9.4.2 ANALYSIS OF THE PRIMARY ENDPOINT

We will use a model-based approach to analyze change in IMAGE-HN score from baseline to 6-month follow-up. Specifically, change in IMAGE-HN score will be modeled using a regression model with a factor for trial arm, covariates for the randomization stratification variable of site and free flap reconstruction, and pre-specified baseline covariates known to be prognostic for the primary endpoint including baseline IMAGE-HN score, gender, education, employment, tumor location, and adjuvant therapy.[8,75] The selection of pre-specified baseline covariates known to be prognostic follows best practices for randomized clinical trials.[103] Additionally, adjusting for the baseline score in a change-score analysis is discussed at length by Frank Harrell and James Slaughter.[104] The GEE regression model was selected to account for the clustering of patients within psychologist (BRIGHT arm) or HN clinical staff member (AC arm). Our preferred model-based approach is a marginal model using GEEs because

subsequent inference best aligns with the trial's stated primary objective. Furthermore, GEEs are robust to variance misspecification. We will use GEEs with an identity link and an exchangeable working correlation structure. Final inference will be based on the robust sandwich estimator.

The primary analysis will use the 6-month IMAGE-HN evaluable set, which eliminates unit non-response, that is, patient data where the baseline or 6-month survey is not completed. However, the potential for survey item non-response exists. There are three types of item non-response to consider: (1) the item is missing at baseline and at follow-up; (2) the item is missing at baseline but not missing at follow-up; and (3) the item is not missing at baseline but is missing at follow-up. We expect the rate of item non-response at baseline to be 0% given training of study coordinators and our experience with the pilot study. In the event of item non-response at the 6-month follow-up, we adopt a conservative imputation approach to avoid inflation of treatment effect. Accordingly, we will impute the baseline value for the given item to reflect no change. As a sensitivity analysis, we will also impute the item's value from the most recent follow-up time prior to 6-months. Finally, depending on the extent of missing data, we may additionally perform sensitivity analyses using multiple imputation or treating survey total scores as interval censored.

To evaluate the inferential impact of our modeling choice (GEE) and cross-sectional (as opposed to longitudinal) data analyses, the following secondary analyses will be conducted using the 6-month IMAGE-HN evaluable set:

1. We will model change in IMAGE-HN score from baseline to 6-month follow-up using a LMER model with a factor for trial arm, the randomization stratification variables of site and free flap reconstruction, and pre-specified baseline covariates including baseline IMAGE-HN score, gender, education, employment, tumor location, and adjuvant therapy. Cluster-specific random effects will be included assuming an exchangeable correlation structure.

2. We will model change in IMAGE-HN score from baseline across all timepoints using GEEs and LMER models as described. Additional model terms for time (discrete), and trial arm-by-time interaction will be included.

All analyses described will be repeated using the per-protocol analysis set.

To evaluate the inferential impact of eliminating unit non-response in our primary analysis, the following additional sensitivity analyses will be performed using the FAS: (1) any trial participant missing the 6-month follow-up survey will be counted as having a 6-month total score equal to the baseline total score (no change from baseline); and (2) any trial participant missing the 6-month follow-up survey will be counted as having a 6-month total score equal to the maximum total score. Trial participants without a baseline survey will be excluded from these analyses.

9.4.3 ANALYSIS OF SECONDARY ENDPOINTS

Secondary endpoints for changes in stigma, depression, anxiety, suicidal ideation, social isolation, and QOL will be analyzed with similar approaches. Covariates prognostic for each of these secondary endpoints will be pre-specified prior to formulation of the final SAP.

We will perform a causal mediation analysis[105] to evaluate the degree to which the effect of treatment (BRIGHT) on the primary outcome (change in IMAGE-HN scores between baseline and 6-month follow-

up) is mediated by changes in candidate mechanism of change variables (between baseline and 3-month follow-up, covariates). We will use structural equation modeling to perform mediation analysis for each of the following mechanism of change variables: (1) BICSI Positive Rational Acceptance score;[55] (2) BICSI Avoidance score;[55] (3) BICSI Appearance Fixing score;[55] and (4) Automatic Thoughts Questionnaire score.[96] This approach allows for ease of interpretation and estimation in Mplus. Model fit will be assessed using chi-square, comparative fit index (>0.95), root mean square of approximation (<0.06), and standardized root mean square residual (<0.08).[106,107] Missing data will be handled with maximum likelihood estimation.[108] If we encounter challenges in model stability, we will use Baron and Kenny's approach.[109] The following regression analyses will be performed: (i) the outcome (IMAGE-HN score) is regressed on a treatment group indicator (BRIGHT, AC) to obtain a regression model measure of the intervention effect; (ii) the candidate mediator (e.g., BICSI Avoidance score) is regressed on the treatment group indicator (BRIGHT, AC) to obtain a measure of the intervention's effect on the covariate; and (iii) the outcome (IMAGE-HN score) is regressed on both the treatment group indicator (BRIGHT, AC) and the candidate mediator (e.g., BICSI Avoidance score). We will conclude that the candidate mediator in fact mediates the effects of the intervention if: (1) in both analyses (i) and (ii), the treatment group indicator is significant; and (2) in analysis (iii), the candidate mediator is significant and the coefficient estimate of the treatment group indicator is smaller in absolute value than its counterpart in analysis (i). If we detect mediation, we will consider Sobel's test to assess the significance of the mediation effect. We will examine standardized coefficients for the direct pathways and the mediation pathways to compare the strength of each. If the cluster effect is significant, we will conduct multilevel mediation analysis for partially nested data.[110] The study design consideration and analytic plan follow recommended criteria to provide evidence for mechanism of change above and beyond statistical mediation.[111] We will also explore mediation analysis using multiple mediators.[112,113] Finally, to better understand the temporal dynamics of causal intervention effects, we will adapt Goldsmith's approach to: (1) examine the intervention effect on outcomes at different time points; (2) examine the intervention effect on hypothesized mediators at different time points; (3) examine the relation of the mediator to the outcome at different time points; and (4) determine if there is temporal variation in the mediating process.[114] If there is temporal variation in the mediating process, we will fit a multilevel mediation model using the approach described by Preacher.[115]

9.4.4 SAFETY ANALYSES

All patients in the SAS will be evaluated for safety and toxicity. Adverse events, SAEs and will be summarized. Safety analyses will include the following summaries:

- AEs, including severity and relationship to a study intervention
- SAEs, including relationship to a study intervention

9.4.5 PLANNED INTERMIN ANALYSES

N/A

9.4.6 SUB-GROUP ANALYSES

Treatment heterogeneity will be evaluated by conducting the following sub-group analyses of the primary and secondary endpoints:

- Age: $\geq$ 65 years vs < 65 years
- Race: white vs non-white

- Gender: male vs female
- Education: ≤ high school vs > high school
- Employment status: disability/unemployed vs working vs retired
- Tumor location: upper aerodigestive tract cancer vs salivary/facial cutaneous cancer
- Reconstruction: non-free flap reconstruction vs free flap reconstruction
- Adjuvant Therapy: none vs radiation therapy/chemoradiation

9.4.7 EXPLORATORY ANALYSES

N/A

9.5 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

9.5.1 SINGLE IRB COORDINATION

The study will be conducted under a single IRB study with MUSC IRB serving as the IRB of record. The MUSC IRB will initiate the reliance agreements with each relying institution, that each relying institution will be responsible for performing a local context review of the study to ensure that the protocol is appropriate and reasonable for their respective study populations. The structure and organization of the study team is shown is described below.

1. **Administrative Sites.** The overall administration of the study will occur at MUSC.

2. **Data Coordinating Sites.** MUSC will serve as the data coordinating site. Study documents will originate from MUSC and be disseminated to each site.

3. **Participating Sites.** In this multisite clinical trial comparing BRIGHT with AC, eligible patients with clinically significant HNC-related BID will be recruited from MUSC, HFH, and WUSM. Study procedures and assessments will be conducted at each site as described in the protocol.

4. **Separate Laboratory and Testing Centers.** There are no separate laboratory and testing centers.

5. **Study Team Composition.** The organization of the study team is shown in **Figure 8**. For the conduct of the trial, the structure of each study team is identical (site PI, psychologist, HNC Clinical staff, and program coordinator).

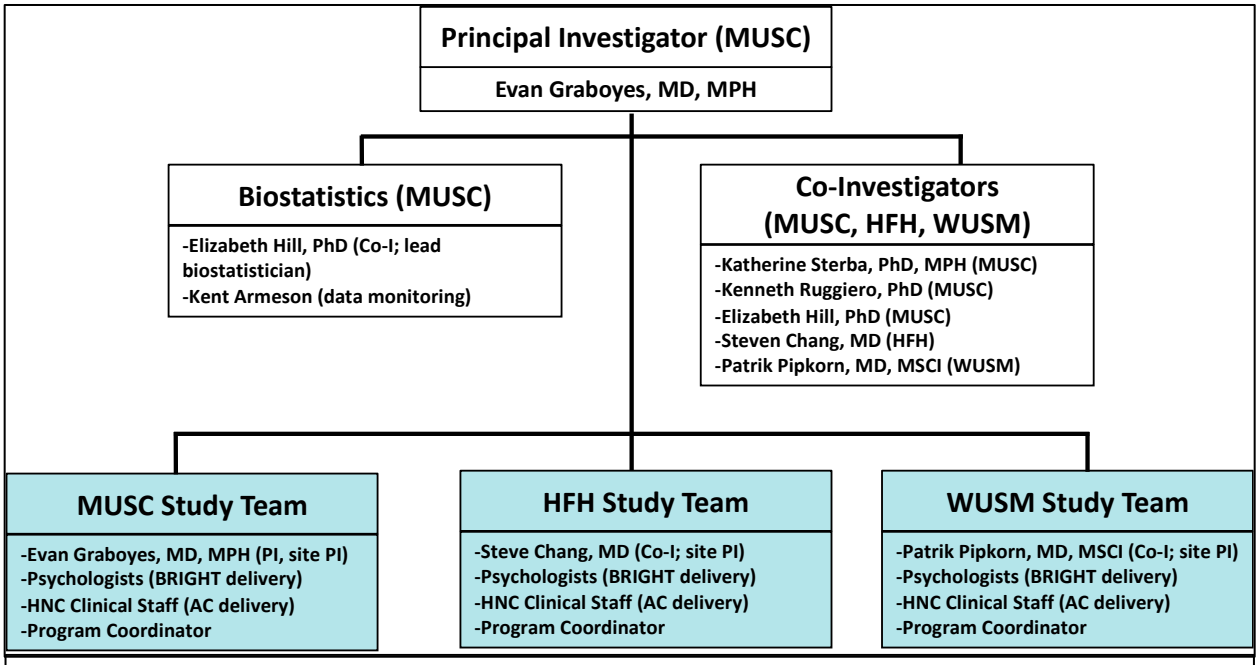


Fig 8. Organization of study team

The study will be coordinated as an sIRB study with the following communication plan. Study documents will be maintained in a HIPAA-compliant and secure shared folder (MUSC Box) to which all non-MUSC study personnel will be given download access. Interactions among sites will be coordinated through site PIs via secure email, telephone call, or video telemedicine sessions (e.g., Microsoft Teams).

9.5.2 INFORMED CONSENT PROCESS

9.5.2.1 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.

9.5.2.2 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 a private research space at each site (if in-person) or via secure telemedicine platform (if electronic informed consent). Only the study participant will provide informed consent. The signed copy of the informed consent document will be stored in the study binder in each patient's section. Subjects will be allowed up to one week to decide whether to participate in the study. If required by the site, 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.

9.5.3 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, or other relevant regulatory or oversight bodies.

9.5.4 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 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.

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.

9.5.5 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.

9.5.6 KEY ROLES AND STUDY GOVERNANCE

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9.5.7 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.

9.5.8 CLINICAL MONITORING

N/A

9.5.9 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 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 9.5.10, 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.

9.5.10 DATA HANDLING AND RECORD KEEPING

9.5.10.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

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

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

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

9.5.10.2 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.

9.5.11 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).

9.5.12 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 9.5.4.**

9.5.13 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.

9.6 ADDITIONAL CONSIDERATIONS

N/A

9.7 ABBREVIATIONS AND SPECIAL TERMS

Table 9. Abbreviations and Special Terms	
AC	Attention Control
AE	Adverse Event
AJCC	American Joint Committee on Cancer
BICSI	Body Image Coping Strategies Inventory
BID	Body Image-Related Distress
CBT	Cognitive Behavioral Therapy
CFR	Code of Federal Regulations
BRIGHT	Building a Renewed ImaGe after Head & neck cancer Treatment
COC	Certificate of Confidentiality
CONSORT	Consolidated Standards of Reporting Trials
DSMP	Data Safety Monitoring Plan
eCRF	Electronic Case Report Form
EHR	Electronic Health Record
EORTC	European Organisation for Research and Treatment of Cancer
FAS	Full Analysis Set
GEE	Generalized Estimating Equation
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
HNC	Head and Neck Cancer
ICC	Intracluster Correlation Coefficient
ICF	Informed Consent Form
ICH	International Council on Harmonisation
IMAGE-HN	Inventory to Measure and Assess imaGe disturbancE-Head & Neck
IRB	Institutional Review Board
ITT	Intention-To-Treat
LMER	Linear Mixed Effect Regression
MUSC	Medical University of South Carolina
MyCB	MyChangedBody
NCI	National Cancer Institute
NCT	National Clinical Trial
NIH	National Institutes of Health
ORHP	Office for Human Research Protections
PI	Principal Investigator
PROM	Patient-Reported Outcome Measure
PRMOIS	Patient-Reported Outcomes Measurement Information System
QOL	Quality of Life
RCT	Randomized Clinical Trial
REDCap	Research Electronic Data Capture
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Safety Analysis Set
SF	Short Form
SOA	Schedule of Activities
SOP	Standard Operating Procedure
UP	Unanticipated Problem

US	United States

9.8 PROTOCOL AMENDMENT HISTORY

Table 10. Protocol Amendment History			
Version	**Date**	**Description of Change**	**Brief Rationale**
2.0	8 December 2022	See attached separate document describing protocol changes	See attached separate document describing protocol changes
3.0	8 February 2023	See attached separate document describing protocol changes	See attached separate document describing protocol changes

10 REFERENCES

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

2. Nekhlyudov L, Lacchetti C, Davis NB, et al. Head and Neck Cancer Survivorship Care Guideline: American Society of Clinical Oncology Clinical Practice Guideline Endorsement of the American Cancer Society Guideline. J Clin Oncol 2017; 35:1606-1621.

3. Fingeret MC, Nipomnick S, Guindani M, Baumann D, Hanasono M, Crosby M. Body image screening for cancer patients undergoing reconstructive surgery. Psychooncology 2014; 23:898-905.

4. Macias D, Hand BN, Pipkorn P, et al. Association of Inventory to Measure and Assess imaGe Disturbance - Head and Neck Scores With Clinically Meaningful Body Image-Related Distress Among Head and Neck Cancer Survivors. Front Psychol 2021; 12:794038.

5. 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.

6. 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.

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. Macias D, Hand BN, Maurer S, et al. Factors Associated With Risk of Body Image-Related Distress in Patients With Head and Neck Cancer. JAMA Otolaryngol Head Neck Surg 2021; 147:1019-1026.

9. Buckwalter AE, Karnell LH, Smith RB, Christensen AJ, Funk GF. Patient-reported factors associated with discontinuing employment following head and neck cancer treatment. Arch Otolaryngol Head Neck Surg 2007; 133:464-470.

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

11. Cognetti DM, Villaflor VM, Fakhry C, Miller MC, Malloy KM. Survivorship support in head and neck cancer: American Head and Neck Society survey. Head Neck 2020.

12. 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.

13. Chen SC, Huang BS, Lin CY, et 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.

14. Melissant HC, Jansen F, Eerenstein SEJ, et al. A structured expressive writing activity targeting body image-related distress among head and neck cancer survivors: who do we reach and what are the effects? Support Care Cancer 2021.

15. Ellis MA, Sterba KR, Brennan EA, et 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.

16. Graboyes EM, Maurer S, Park Y, et al. Evaluation of a novel telemedicine-based intervention to manage body image disturbance in head and neck cancer survivors. Psychooncology 2020; 29:1988-1994.

17. Folkman S. Positive psychological states and coping with severe stress. Soc Sci Med 1997; 45:1207-1221.

18. David D, Montgomery GH. The Scientific Status of Psychotherapies: A New Evaluative Framework for Evidence-Based Psychosocial Interventions. Clin Psychol Sci Prac 2011; 18:89-99.

19. David D, Szentagotai A. Cognitions in cognitive-behavioral psychotherapies; toward an integrative model. Clin Psychol Rev 2006; 26:284-298.

20. Murphy R, Cooper Z, Hollon SD, Fairburn CG. How do psychological treatments work? Investigating mediators of change. Behav Res Ther 2009; 47:1-5.

21. Powers MB, de Kleine RA, Smits JAJ. Core Mechanisms of Cognitive Behavioral Therapy for Anxiety and Depression: A Review. Psychiatr Clin North Am 2017; 40:611-623.

22. Dobson KS. The science of CBT: toward a metacognitive model of change? Behav Ther 2013; 44:224-227.

23. Hofmann SG, Asmundson GJ, Beck AT. The science of cognitive therapy. Behav Ther 2013; 44:199-212.

24. Cash TF, Smolak L. Body Image: A Handbook of Science, Practice, and Prevention. New York: Guilford Press, 2012:490.

25. Kayser K, Brydon DM, Moon H, Zebrack B. Institutional capacity to provide psychosocial care in cancer programs: Addressing barriers to delivering quality cancer care. Psychooncology 2020; 29:1995-2002.

26. Wampold BE. How important are the common factors in psychotherapy? An update. World Psychiatry 2015; 14:270-277.

27. Graboyes EM, Hand BN, Ellis MA, et al. Validation of a Novel, Multidomain Head and Neck Cancer Appearance- and Function-Distress Patient-Reported Outcome Measure. Otolaryngol Head Neck Surg 2020; 163:979-985.

28. Miller KD, Nogueira L, Mariotto AB, et al. Cancer treatment and survivorship statistics, 2019. CA Cancer J Clin 2019; 69:363-385.

29. Tota JE, Best AF, Zumsteg ZS, Gillison ML, Rosenberg PS, Chaturvedi AK. Evolution of the Oropharynx Cancer Epidemic in the United States: Moderation of Increasing Incidence in Younger Individuals and Shift in the Burden to Older Individuals. J Clin Oncol 2019; 37:1538-1546.

30. Melissant HC, Jansen F, Eerenstein SE, et al. Body image distress in head and neck cancer patients: what are we looking at? Support Care Cancer 2021; 29:2161-2169.

31. Kissane DW, Patel SG, Baser RE, et 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.

32. Branch L, C. F, McQuestion M. An Investigation into Body Image Concerns in the Head and Neck Cancer Population Receiving Radiation or Chemoradiation Using the Body Image Scale: A Pilot Study. Journal of Medical Imaging and Radiation Sciences 2017; 48:169-165.

33. Clarke SA, Newell R, Thompson A, Harcourt D, Lindenmeyer A. Appearance concerns and psychosocial adjustment following head and neck cancer: A cross-sectional study and nine-month follow-up. Psychol Health Med 2014; 19:505-518.

34. Chen SC, Yu PJ, Hong MY, et al. Communication dysfunction, body image, and symptom severity in postoperative head and neck cancer patients: factors associated with the amount of speaking after treatment. Support Care Cancer 2015; 23:2375-2382.

35. Hung TM, Lin CR, Chi YC, et al. Body image in head and neck cancer patients treated with radiotherapy: the impact of surgical procedures. Health Qual Life Outcomes 2017; 15:165.

36. Chen C, Cao J, Wang L, Zhang R, Li H, Peng J. Body image and its associated factors among Chinese head and neck cancer patients undergoing surgical treatment: a cross-sectional survey. Support Care Cancer 2019.

37. 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.

38. 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.

39. 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.

40. Graboyes EM, Hill EG, Marsh CH, et al. Temporal Trajectory of Body Image Disturbance in Patients with Surgically Treated Head and Neck Cancer. Otolaryngol Head Neck Surg 2020; 162:304-312.

41. Sherman KA, Przezdziecki A, Alcorso J, et 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.

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

43. 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.

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

45. Alleva JM, Sheeran P, Webb TL, Martijn C, Miles E. A Meta-Analytic Review of Stand-Alone Interventions to Improve Body Image. PLoS One 2015; 10:e0139177.

46. Lewis-Smith H, Diedrichs PC, Halliwell E. Cognitive-behavioral roots of body image therapy and prevention. Body Image 2019; 31:309-320.

47. Blashill AJ, Safren SA, Wilhelm Set al. Cognitive behavioral therapy for body image and self-care (CBT-BISC) in sexual minority men living with HIV: A randomized controlled trial. Health Psychol 2017; 36:937-946.

48. Newell RJ. Altered body image: a fear-avoidance model of psycho-social difficulties following disfigurement. J Adv Nurs 1999; 30:1230-1238.

49. Bessell A, Brough V, Clarke A, Harcourt D, Moss TP, Rumsey N. Evaluation of the effectiveness of Face IT, a computer-based psychosocial intervention for disfigurement-related distress. Psychol Health Med 2012; 17:565-577.

50. Faraji J, Mahdavi A, Samkhaniyan E, Asadi SH, Dezhkam N. A review of the effectiveness of cognitive-behavioral group therapy on the reduction of body image concern in patients with breast cancer. J Med Life 2015; 8:82-86.

51. Fadaei S, Janighorban M, Mehrabi T, Ahmadi SA, Mokaryan F, Gukizade A. Effects of cognitive behavioral counseling on body Image following mastectomy. J Res Med Sci 2011; 16:1047-1054.

52. Hummel SB, van Lankveld J, Oldenburg HAS, et al. Efficacy of Internet-Based Cognitive Behavioral Therapy in Improving Sexual Functioning of Breast Cancer Survivors: Results of a Randomized Controlled Trial. J Clin Oncol 2017; 35:1328-1340.

53. Lewis-Smith H, Diedrichs PC, Rumsey N, Harcourt D. Efficacy of psychosocial and physical activity-based interventions to improve body image among women treated for breast cancer: A systematic review. Psychooncology 2018; 27:2687-2699.

54. Bessell A, Moss TP. Evaluating the effectiveness of psychosocial interventions for individuals with visible differences: a systematic review of the empirical literature. Body Image 2007; 4:227-238.

55. 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.

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

57. Cho J, Fingeret MC, Huang SC, Liu J, Reece GP, Markey MK. Observers' response to facial disfigurement from head and neck cancer. Psychooncology 2018.

58. Klimek P, Wilhelm S, Safren SA, Blashill AJ. Cognitive Behavioral Therapy for Body Image and Self-Care (CBT-BISC) among Sexual Minority Men Living with HIV: Skills-Based Treatment Mediators. Cognit Ther Res 2020; 44:208-215.

59. Melnyk SE, Cash TF, Janda LH. Body image ups and downs: prediction of intra-individual level and variability of women's daily body image experiences. Body Image 2004; 1:225-235.

60. Blakey SM, Reuman L, Buchholz JL, Abramowitz JS. Experiential avoidance and dysfunctional beliefs in the prediction of body image disturbance in a nonclinical sample of women. Body Image 2017; 22:72-77.

61. Yamani Ardakani B, Tirgari B, Roudi Rashtabadi O. Body image and its relationship with coping strategies: The views of Iranian breast cancer women following surgery. Eur J Cancer Care (Engl) 2020; 29:e13191.

62. Stefan S, Cristea IA, Szentagotai Tatar A, David D. Cognitive-behavioral therapy (CBT) for generalized anxiety disorder: Contrasting various CBT approaches in a randomized clinical trial. J Clin Psychol 2019; 75:1188-1202.

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

64. David JM, Ho AS, Luu M, et 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.

65. Graboyes EM, Ellis MA, Li H, et 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.

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

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

68. 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.

69. 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.

70. 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.

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

72. 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.

73. 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.

74. 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.

75. Graboyes EM, Maurer S, Balliet W, et al. Efficacy of a Brief Tele-Cognitive Behavioral Treatment vs Attention Control for Head and Neck Cancer Survivors With Body Image Distress: A Pilot Randomized Clinical Trial. JAMA Otolaryngol Head Neck Surg 2022.

76. Hatcher RL, Gillaspy JA. Development and validation of a revised short version of the Working Alliance Inventory. Psychotherapy Research 2006; 16:12–25.

77. Nilsen ML, Clump DA, 2nd, Kubik M, et al. Prevision of multidisciplinary head and neck cancer survivorship care during the 2019 novel coronavirus pandemic. Head Neck 2020; 42:1668-1673.

78. Huang VW, Imam SA, Nguyen SA. Head and neck survivorship care in the times of the SARS-CoV-2 pandemic. Head Neck 2020; 42:1664-1667.

79. Greenbaum Z. How well is telepsychology working? Available at: *https://www.apa.org/monitor/2020/07/cover-telepsychology. Accessed April 8 2021*.

80. Murphy R, Calugi S, Cooper Z, Dalle Grave R. Challenges and Opportunities for enhanced cognitive behaviour therapy (CBT-E) in light of COVID-19. The Cognitive Behaviour Therapist 2020:1-31.

81. Crawford A, Serhal E. Digital Health Equity and COVID-19: The Innovation Curve Cannot Reinforce the Social Gradient of Health. J Med Internet Res 2020; 22:e19361.

82. Holmes C. Guide to Finding the Best Cell Phone Coverage. March 2, 2021. Available at: https://www.whistleout.com/CellPhones/Guides/Coverage. Accessed April 1 2021.

83. Carroll KM, Rounsaville BJ. Efficacy and effectiveness in developing treatment manuals. In: Nezu AM, Nezu CM, eds. Evidence-Based Outcome Research: A Practical Guide to Conducting Randomized Controlled Trials of Psychosocial Interventions. New York: Oxford University Press, 2008.

84. Freedland KE, King AC, Ambrosius WT, et al. The selection of comparators for randomized controlled trials of health-related behavioral interventions: recommendations of an NIH expert panel. J Clin Epidemiol 2019; 110:74-81.

85. Waller G, Stringer H, Meyer C. What cognitive behavioral techniques do therapists report using when delivering cognitive behavioral therapy for the eating disorders? J Consult Clin Psychol 2012; 80:171-175.

86. Carroll KM, Nich C, Sifry RLet al. A general system for evaluating therapist adherence and competence in psychotherapy research in the addictions. Drug Alcohol Depend 2000; 57:225-238.

87. Hansen WB, Malotte CK, Fielding JE. The bogus pipeline revisited: the use of the threat of detection as a means of increasing self-reports of tobacco use. J Appl Psychol 1985; 70:789-792.

88. Norman GR, Sloan JA, Wyrwich KW. Interpretation of changes in health-related quality of life: the remarkable universality of half a standard deviation. Med Care 2003; 41:582-592.

89. Pilkonis PA, Choi SW, Reise SP, et 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.

90. Beck AT, Steer RA, Ranieri WF. Scale for Suicide Ideation: psychometric properties of a self-report version. J Clin Psychol 1988; 44:499-505.

91. Beck AT, Steer RA. Manual for the Beck Scale for Suicide Ideation. San Antonio, TX: Psychological Corporation, 1991.

92. Beck AT, Brown GK, Steer RA, Dahlsgaard KK, Grisham JR. Suicide ideation at its worst point: a predictor of eventual suicide in psychiatric outpatients. Suicide Life Threat Behav 1999; 29:1-9.

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

94. Bode RK, Hahn EA, DeVellis R, Cella D, Patient-Reported Outcomes Measurement Information System Social Domain Working G. Measuring participation: the Patient-Reported Outcomes Measurement Information System experience. Arch Phys Med Rehabil 2010; 91:S60-65.

95. Bjordal K, de Graeff A, Fayers PM, et al. A 12 country field study of the EORTC QLQ-C30 (version 3.0) and the head and neck cancer specific module (EORTC QLQ-H&N35) in head and neck patients. EORTC Quality of Life Group. Eur J Cancer 2000; 36:1796-1807.

96. Netemeyer RG, Williamson DA, Burton S, Biswas D, Jindal S, Landreth S. Psychometric properties of shortened versions of the automatic thoughts questionnaire. Educational and Psychological Measurement 2002; 62:111-129.

97. Decker SE, Nich C, Carroll KM, Martino S. Development of the Therapist Empathy Scale. Behav Cogn Psychother 2014; 42:339-354.

98. Devilly GJ, Borkovec TD. Psychometric properties of the credibility/expectancy questionnaire. J Behav Ther Exp Psychiatry 2000; 31:73-86.

99. Duggan C, Parry G, McMurran M, Davidson K, Dennis J. The recording of adverse events from psychological treatments in clinical trials: evidence from a review of NIHR-funded trials. Trials 2014; 15:335.

100. 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.

101. Eldridge SM, Ashby D, Feder GS, Rudnicka AR, Ukoumunne OC. Lessons for cluster randomized trials in the twenty-first century: a systematic review of trials in primary care. Clin Trials 2004; 1:80-90.

102. Baldwin SA, Murray DM, Shadish WRet al. Intraclass correlation associated with therapists: estimates and applications in planning psychotherapy research. Cogn Behav Ther 2011; 40:15-33.

103. Adjusting for Covariates in Randomized Clinical Trials for Drugs and Biological Products, Guidance for Industry, Revision 1. In: US Department of Health and Human Services FaDA, Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research, ed., 2021.

104. Harrell FE, Slaughter JC. Biostatistics for Biomedical Research. In: Slaughter FHJ, ed., 2022.

105. MacKinnon DP, Fairchild AJ, Fritz MS. Mediation analysis. Annu Rev Psychol 2007; 58:593-614.

106. Kline RB. Principles and Practice of Structural Equation Modeling. New York, NY: The Guilford Press, 2016.

107. Hooper D, Coughlan J, Mullen M. Structural Equation Modelling: Guidelines for Determining Model Fit. Electronic Journal of Business Research Methods 2008; 6:53-60.

108. Molenberghs G, Kenward MG. Missing Data in Clinical Studies. West Sussex, England: John Wiley & Sons, 2007.

109. Baron RM, Kenny DA. The moderator-mediator variable distinction in social psychological research: conceptual, strategic, and statistical considerations. J Pers Soc Psychol 1986; 51:1173-1182.

110. Lachowicz MJ, Sterba SK, Preacher KJ. Investigating multilevel mediation with fully or partially nested data. Group Processes & Intergroup Relations 2015; 18:274-289.

111. Kazdin AE. Mediators and mechanisms of change in psychotherapy research. Annu Rev Clin Psychol 2007; 3:1-27.

112. Daniel RM, De Stavola BL, Cousens SN, Vansteelandt S. Causal mediation analysis with multiple mediators. Biometrics 2015; 71:1-14.

113. VanderWeele TJ, Vansteelandt S. Mediation Analysis with Multiple Mediators. Epidemiol Methods 2014; 2:95-115.

114. Goldsmith KA, MacKinnon DP, Chalder T, White PD, Sharpe M, Pickles A. Tutorial: The practical application of longitudinal structural equation mediation models in clinical trials. Psychol Methods 2018; 23:191-207.

115. Preacher KJ, Zyphur MJ, Zhang Z. A general multilevel SEM framework for assessing multilevel mediation. Psychol Methods 2010; 15:209-233.