Mental Health App for Cancer Survivors Study (MACS Study)

2/10/2025

NCT06472726

Carbone Cancer Center
UNIVERSITY OF WISCONSIN
SCHOOL OF MEDICINE AND PUBLIC HEALTH

Mental Health App for Cancer Survivors Study (MACS Study)

Protocol Number: IRB /Other Protocol Number
Principal Investigator: Earlise C. Ward, PhD, LP

Funding: NCI Head and Neck Cancer SPORE at the University of Wisconsin –NCI P50CA278595

Protocol Version History

Protocol Version	Version Date	Summary of Revisions Made	Rationale
1.0	mm/dd/yyyy	Initial version	
2.0	08/07/2024	Update study windows	Clarification
3.0	02/10/2025	Allowed for re-approach and lowered PHQ-9 eligibility	Increase recruitment

Table of Contents

1.0 STATEMENT OF COMPLIANCE

I confirm that I have read this protocol. I will comply with the IRB-approved protocol, and applicable regulations, guidelines, laws, and institutional policies.

I agree to ensure that all staff members involved in the conduct of this study are informed about their obligations in meeting the above commitment.

Name	**Signature**	**Date**
Principal Investigator		

2.0 LIST OF ABBREVIATIONS

AE	Adverse Event
AI	Artificial Intelligence
CBT	Cognitive Behavioral Therapy
CFR	Code of Federal Regulations
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
CTMS	Clinical Trial Management Software
DHHS	Department of Health and Human Services
DMC	Data Monitoring Committee
DSMB	Data & Safety Monitoring Board
DSMC	Data & Safety Monitoring Committee
DSMP	Data & Safety Monitoring Plan
eCRF	Electronic Case Report Forms
EDC	Electronic Data Capture
EHR	Electronic Health Record
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
HNC	Head and Neck Cancers
HPV	Human Papillomavirus
ICTR	Institute for Clinical and Translational Research
IRB	Institutional Review Board
LiCBT	Low-Intensity Cognitive Behavioral Therapy
NCI	National Cancer Institute
NIH	National Institutes of Health
OHRP	Office for Human Research Protections
OnCore	Online Collaborative Research Environment
PHI	Protected Health Information
PHQ-9	Patient Health Questionnaire-9
PI	Principal Investigator
PRO	Patient-Reported Outcome
REDCap	Research Electronic Data Capture
SAE	Serious Adverse Event
SCC	Squamous Cell Carcinoma
SHOW	Survey of the Health of Wisconsin
SUS	System Usability Scale
UP	Unanticipated Problem
UWCCC	University of Wisconsin Carbone Cancer Center

3.0 STUDY SYNOPSIS

Full Title	Mental Health App for Cancer Survivors Study (MACS Study)
Short Title	Mental Health App for Cancer Survivors Study (MACS Study)
Protocol Number	IRB 2024-0111
ClinicalTrials.gov Identifier & Summary	NCT06472726 This study is being done to estimate the feasibility/efficacy/acceptability of the IONA Mind app for head and neck cancer (HNC) patients and survivors who show evidence of comorbid depression. In partnership with the UWCCC, the IONA Mind Team, the Survey of the Health of Wisconsin (SHOW) and the Head Neck Patient Advocacy team, we propose adaptation of the IONA Mind app and pilot testing the app with 30 HNC patients and survivors. Using a mixed method design the specific aims are: AIM 1. Adaptation of IONA Mind app for head and neck cancer. The research team will iteratively adapt the IONA Mind app to provide psychological support for HNC patients and survivors. The HNC Survivors Advisory Board will assist in identifying key aspects of the HNC survivors' journey from diagnosis to the survivorship phase, which will be prioritized and considered to iteratively redesign the IONA Mind phone app to better support HNC patients and survivors; AIM 2. Identify feasibility of the IONA Mind app for head and neck cancer. The IONA Mind app will be tested with 30 HNC patients and survivors, recruited from the Survey of the Health of Wisconsin (SHOW) recruitment registry and from the clinical practice at UW Carbone Cancer Center (UWCCC); AIM 3. Determine preliminary efficacy IONA Mind app tailored for depression comorbid with head and neck cancer. Clinical outcomes will be measured at baseline, weekly for 6 weeks (including the 6-week period of app utilization), and post-intervention follow-up conducted at 1- and 3-month post intervention using validated tools to access depression; AIM 4. Determine satisfaction and acceptability of the IONA Mind app. Satisfaction with the IONA Mind app will be measured with the System Usability Scale (SUS) delivered at 1-2 weeks following the completion of the app utilization. In addition, a qualitative interview for a random sub sample of 10 - 15 participants will occur shortly after completion of the intervention to assess satisfaction with and acceptability of the mobile app. A head and neck patient and survivor phone app LiCBT intervention to treat depression co-designed by HNC advocates, mental health professionals and an expert technologist is a critical outcome of this research.
Number of Site(s)	One site: University of Wisconsin-Madison
Phase	Not applicable.
Main Inclusion Criteria	• History of HNC confirmed by histopathologic diagnosis. The signed report must be available on EHR for participants who received treatment or follow-up at University of Wisconsin Carbone Cancer Center (UWCCC). Alternatively, participants must have a printed signed report if received treatment out of UWCCC • Age ≥ 22 years at the time of consent. • Patient Health Questionnaire-9 (PHQ-9) score ≥ 5 and ≤ 19 (mild, moderate and severely moderate depression) • Willing to comply with all study procedures and be available for the duration of the study.
Main Exclusion Criteria	• Unable to read and speak English. • Utilization of prescription medicine to treat depression for fewer than 7 weeks. • Patient Health Questionnaire-9 (PHQ-9) score of ≥20 (severe depression) • Patient Health Questionnaire-9 (PHQ-9) score ≥1 on the suicidal question (question 9) • Pregnant people

Objective(s)	Primary Objectives • To adapt the IONA Mind app to be tailored for depression in HNC patients and survivors. • To identify feasibility of the IONA Mind app tailored for depression comorbid with HNC in HNC patients and survivors. • To determine preliminary efficacy of the IONA Mind app tailored for depression comorbid with HNC in HNC patients and survivors. • To determine satisfaction and acceptability of the IONA Mind app tailored for depression comorbid with HNC in HNC patients and survivors.
Endpoints	Primary Endpoint • The research team will iteratively adapt the IONA Mind app to provide psychological support for HNC patients and survivors by working with the HNC Survivors Advisory Board and the IONA Mind app builders. The iteration of the IONA Mind app that will be used in the pilot trial is that which the HNC Survivors Advisory Board agrees is adequate to support HNC patients and survivors. • Feasibility of IONA Mind app utilization will be assessed by our Recruitment and Retention Tracking tool that documents the number of individuals screened, recruited, dropped out (and reasons for), refused, and not eligible for the study, and duration of IONA Mind app utilization. • Clinical outcomes will be measured at baseline, weekly for 6 weeks during app utilization, and at post-intervention follow-up conducted at 1- and 3-month post intervention using the PHQ-9. • Satisfaction with the IONA Mind app will be measured with the System Usability Scale (SUS)[20] delivered on REDCap at 1-2 weeks following the completion of the app utilization. • Acceptability as well as satisfaction will be ascertained via a qualitative semi-structured interview for a random subsample of 10 - 15 participants after completion of the intervention (1-2 weeks post-intervention).
Study Design	Prospective single-arm pilot study.
IND or IDE Number	Not applicable.
FDA Regulatory Overview	Not applicable.
Study Intervention	IONA Mind is a digital app that delivers mental health support. Once users sign up and respond to the initial assessment with PHQ-9 questionnaire, it reaches out to users proactively to offer support, personalized wellbeing plans, and guidance. The tool is available 24 hours, 7 days a week.
Total Number of Subjects	The accrual goal is 30 participants total including HNC patients newly diagnosed, undergoing treatment, post treatment follow-up, and HNC survivors.
Study Population	Male and female HNC patients and survivors aged 22 years and older with comorbid depression, as evidenced by a score ≥ 5 and ≤ 19 on the PHQ-9.
Statistical Methodology	To test the hypotheses that the utilization of the IONA Mind app will reduce levels of depression, we propose a linear mixed model with random effects specified. Predictive margins and margins plots will be used to graphically display the impact of IONA Mind app on levels of depression.
Estimated Subject Duration	Approximately 5 months: The intervention period is 6 weeks, clinical outcomes will be assessed for 6 weeks, with a 1- and 3-month follow-up assessment with PHQ-9.

Estimated Enrollment Period & Study Duration	Study enrollment and follow-up will occur over 7 months with the total expected duration of the trial to be 12 months.

4.0 KEY ROLES

The following is a list of all key personnel and roles:

Principal Investigator	Earlise C. Ward, MS, PhD, LP Professor, Department of Family Medicine and Community Health Faculty Director, Cancer Health Disparities Initiative (CHDI) SMPH/Carbone Cancer Center Whitney Way N 610, Madison, WI 53705 Phone: 608-262-7917 Email: *earlise.ward@fammed.wisc.edu*
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Field Team Supervisor	Doug Esselman, BS Field Team Supervisor Survey of the Health of Wisconsin (SHOW) Email: *djesselman@show.wisc.edu*
Survivorship Research Program/ Cancer Health Disparities Initiative	Cibele Barbosa Carroll, MD, Ph.D. Scientist II SMPH/Carbone Cancer Center 610 Walnut ST – WARF, room 370 Madison, WI 53726-2336 Phone: (608)421-3190 Email: *barbosacarro@wisc.edu*
Outreach Specialist Patient Navigator	Lucretia Sullivan Wade Cancer Health Disparities Initiative UW Carbone Cancer Center 610 N. Walnut St., WARF 370 Madison, WI 53726 Phone: (608) 262-7917 Email: *sullivanwade@wisc.edu*
Participating Site(s)	University of Wisconsin-Madison
Data and Safety Monitoring Board	Committee Name Institution Email
NIH Point of Contact	Name, degree Title Institution Name Address Phone Number Email
Biostatistician	Amy Schultz, PhD Senior Epidemiology Data Scientist, Informatics and IT Associate Director, Survey of the Health of Wisconsin School of Medicine and Public Health University of Wisconsin - Madison Phone: (815) 307-4007 Email: aaschultz4@wisc.edu

5.0 INTRODUCTION

5.1 Disease Background

Head and neck cancers (HNC) represent the 7th most common cancer worldwide.[1,2] Squamous cell carcinoma (SCC) is the histologic type in nearly 90% of cases and, in general, arises in the context of heavy smoking and chronic alcohol use.[1,2] More recently, human papillomavirus (HPV) has been associated with oropharyngeal cancers[1,2] while the Epstein-Barr virus has been associated with nasopharyngeal carcinomas.[2] Soft tissue and bone sarcomas of the HNC are rare, representing approximately 2% of all HNC types, and may arise after head and neck radiation exposure.[3]

Head and neck SCC and sarcomas usually require multimodality treatments and frequently affect critical functions such as breathing, speaking, swallowing, and eating.[2] Long-term effects like xerostomia and thick saliva are common following radiation therapy.[4] Although these adverse effects may improve over time, they often cause discomfort for survivors by interfering with swallowing, speaking, and oral health.[4] Besides functional impairments, HNC survivors often experience altered appearance due to cancer, due to the preparation to undergo cancer treatments (teeth extraction, placement of feeding devices) and due to cancer therapies.[5-7] Moreover, appearance change can result from weight loss associated with long-term and late effects of treatments.[7,8] An altered appearance may cause patients to regret the decision of undergoing surgical treatment and suffer from self-image issues.[7]

Each one of the long-term and late adverse effects of treatments, individually or combined, may interfere with the individual's ability to participate in social life and employment activities to the same degree it occurred before having cancer. All the changes imposed by HNC and oncological treatments, and the need to adapt to the "new normal," often cause distress, anxiety, and depression.[5,9] The prevalence of depression among HNC survivors may be as high as 52% during treatment, 48.3% 6-months after treatment, and 27% 3-years post-diagnosis.[10] Some researchers report HNC as one of the most psychologically distressing and traumatic of all cancers, with reported suicide rates of 63.4 per 100,000 person-years.[9] The suicide rate among HNC survivors is nearly 4 times higher than the suicide rate among individuals without cancer and 2 times higher than the rate among cancer survivors in general.[9] Some guidelines for HNC care recommend distress screening.[6] Others suggest psychological support when clinically indicated.[11] The prevalence of depression among HNC patients and survivors illustrate the need for multidisciplinary interventions to better support patients and survivors of HNC.

Individuals with a cancer diagnosis may face multiple sources of distress (fear of recurrence, managing cancer or cancer treatment adverse effects, job insecurity, etc.).[12] Distress in cancer is a multifactorial unpleasant experience often originating from psychological, social, spiritual, and or physical aspects that might affect the ability to cope with the experience of having cancer.[12] Distress may range from feelings of sadness and vulnerability to incapacitating problems such as depression, anxiety, and panic, depending on individuals' personality characteristics, resilience, and coping mechanisms.[12] Research suggests the emotional burden of cancer is evident in the high rates of depression, anxiety, and distress among patients with cancer. The NCCN Distress Guidelines recommend that cancer survivors should be screened for distress. Survivors with clinical evidence of moderate to severe distress should be referred to psychological/psychiatric support, social work, counseling services, and or chaplaincy care.[12] In addition, the guideline recommends that oncology practices should have licensed mental health professionals available for cancer survivors as staff members or referrals.[12] Cognitive Behavioral Therapy (CBT) is an evidence-based psychosocial treatment to help manage distress among cancer survivors.[12] In CBT, cognitive methods are utilized to reframe the patient's mental environment, while behavioral methods are applied to change the patient's interactions with the external environment.[13]

Low intensity Cognitive Behavioral Therapy (LiCBT) is an evidenced-based psychological treatment for mild to moderate depression and anxiety.[14] In addition, a meta-analysis comparing 16 studies of low intensity interventions to treat depression showed that patients with more severe depression also experience clinical benefits from LICBT.[15] The treatment is based on health technologies in the form of book or computer-based

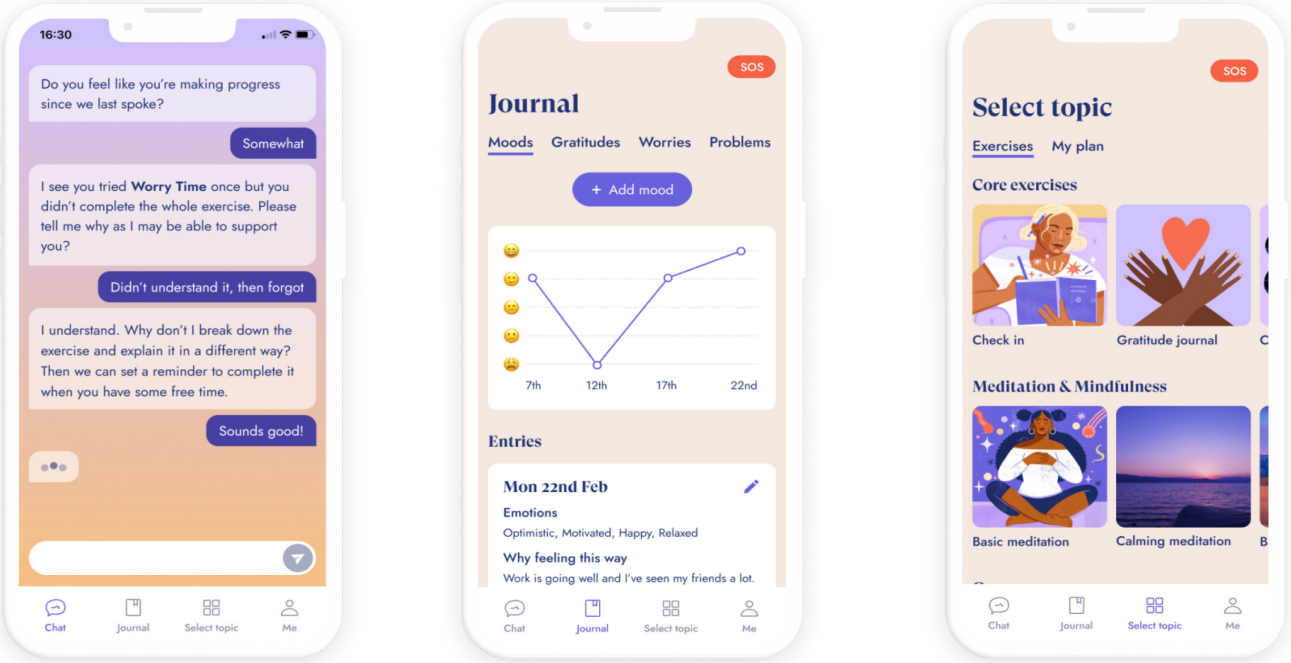
self-help interventions and can be supported face-to-face, on the telephone or by email.[14] Within the National Health Service (NHS) in England, LiCBT is fundamental to the NHS Talking Therapies service where it is supported at Step 2 of a stepped care service delivery model by a psychological wellbeing practitioner rather than psychologist or therapist workforce. The approach thereby facilitates access to evidence-based psychological therapies at reduced personal impact for the patient while placing fewer resource demands on health care systems. Given the success of NHS Talking Therapies there is significant expansion, with LiCBT being increasingly adopted as part of service delivery on an international level and in different contexts such as physical health settings.

5.2 IONA Mind LiCBT

IONA Mind is a mental health phone app that offers potential to increase access to evidence-based psychological therapy. Not only does it support the delivery of techniques derived from LiCBT, but it also addresses wider barriers to accessing psychological therapy such as the desire to handle the problem on one's own, stigma, and limited willingness to disclose problems.[16] Further developments in LiCBT are evident with such that LiCBT interventions have moved onto a mobile phone-based platform. Given the expertise of our research team we have been given an opportunity to work with IONA Mind, an American-based mobile technology company and in collaboration with Dr. Paul Farrand at the University of Exeter, UK to develop and evaluate a LiCBT phone app for the treatment of depression in people with HNC. Our collaboration with IONA Mind is aiming to develop a mental health phone app that offers potential to increase access to evidence-based psychological therapy. A significant innovation within the IONA Mind app is the development of Artificial Intelligence (AI)-driven automated support that adjusts itself to user progress.

Following app download in the device of preference (phone or ipad), the IONA Mind user completes depression assessments with Patient Health Questionnaire-9 (PHQ-9). The app will suggest CBT practices accordingly. Figure 1 provides an overview of IONA Mind activities. Providing AI-driven support in use on the app offers potential to provide a scalable solution for the treatment of depression among patients receiving treatment for HNC, as well as among survivors. Additionally, when adapted to meet the needs of specific populations, the app improves treatment acceptability which is correlated with improving mental health outcomes.

Figure 1. The IONA Mind LICBT app overview



IONA Mind app contains evidence-based, protocol driven mental health plans which are delivered algorithmically over the course of 6 weeks. The app personalizes the interventions to the patients. Automated (AI) support is delivered via a chatbot. Patient progress through the course is measured in the progress tab and recorded in the app.

5.3 Rationale

Considering the prevalence of depression among HNC patients and survivors and the LiCBT potential to increase access to mental health treatment and outcomes, we propose a pilot feasibility study adapting and utilizing the IONA Mind LiCBT digital app to support patients and survivors of HNC.

6.0 STUDY OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To adapt the IONA Mind app to be tailored for depression in HNC patients and survivors.	• The research team will iteratively adapt the IONA Mind app to provide psychological support for HNC patients and survivors by working with the HNC Survivors Advisory Board and the IONA Mind app builders. The iteration of the IONA Mind app that will be used in the pilot trial is that which the HNC Survivors Advisory Board agrees is adequate to support HNC patients and survivors.
• To identify feasibility of the IONA Mind app tailored for depression comorbid with HNC in HNC patients and survivors.	• Feasibility of IONA Mind app utilization will be assessed by our Recruitment and Retention Tracking tool that documents the number of individuals screened, recruited, dropped out (and

Objectives	Endpoints
	reasons for), refused, and not eligible for the study, and duration of IONA Mind app utilization.
• To determine preliminary efficacy of the IONA Mind app tailored for depression comorbid with HNC in HNC patients and survivors.	• Clinical outcomes will be measured at baseline, weekly for 6 weeks during the app utilization, and at post-intervention follow-up conducted at 1- and 3-month post intervention using the PHQ-9.
• To determine satisfaction and acceptability of the IONA Mind app tailored for depression comorbid with HNC in HNC patients and survivors.	• Satisfaction with the IONA Mind app will be measured with the System Usability Scale (SUS) delivered on REDCap at 1-2 weeks following the completion of the app utilization. • Acceptability as well as satisfaction will be ascertained via a qualitative semi-structured interview after completion of the intervention (1-2 weeks post-intervention).

7.0 STUDY DESIGN

7.1 General Design

This prospective single-arm pilot study will test the IONA Mind app with 30 HNC patients and survivors, recruited from the Survey of the Health of Wisconsin (SHOW)[17] recruitment registry and from the clinical practice at UW Carbone Cancer Center (UWCCC). Enrolled subjects will utilize the redesigned IONA Mind app for a 6-week period and submit self-reported generated data using the nine-item measure of depression, PHQ-9. Final follow-up assessment with PHQ-9 will occur at 1- and 3-month following the completion of app utilization.

After critical input from the UWCCC HNC Survivors Advisory Board in the redesign of the IONA Mind app (see section 9.2, Adaptation of IONA Mind App for HNC), this pilot study will test the feasibility, preliminary effectiveness, satisfaction and acceptability of the IONA Mind app utilization. Subject accrual will occur over 7 months with the total duration of the trial expected to be 12 months.

7.2 End of Study Definition

The end of the study is defined as the date of completion of any final follow-up activity or data collection described in the protocol. See Appendix A for study timeline.

8.0 SUBJECT SELECTION

8.1 Inclusion & Exclusion Criteria

Eligibility will be determined by inclusion and exclusion criteria below and confirmed by medical record review as necessary.

Inclusion Criteria
1. Ability to understand and the willingness to sign a written informed consent document.
2. History of HNC confirmed by histopathologic diagnosis. The signed report must be available on EHR for participants who received treatment or follow-up at UWCCC. Alternatively, participants must have a printed signed report if received treatment outside of UWCCC.
3. Age ≥ 22 years.

Inclusion Criteria
4. PHQ-9 score ≥ 5 and ≤ 19.
5. Willing to comply with all study procedures and be available for the duration of the study.

Exclusion Criteria
1. Unable to read and speak English.
2. Utilization of prescription medicine to treat depression for fewer than 7 weeks.
3. Currently receiving psychological therapy treatment for depression
4. 4. Pregnant People
• PHQ-9 score ≥ 20. As indicated in the research protocol, the PHQ-9 will be used for screening for inclusion and exclusion. PHQ-9 scores of 5-9 (mild), 10-14 (moderate), 15-19 (moderately severe) and 20-27 (severe) represent thresholds. Individuals who screen severe with a score of 20-27 will be informed that they are not eligible for the study due to severity of symptoms. In addition, Patient Health Questionnaire-9 (PHQ-9) score ≥1 on the suicidal question (question 9) will be excluded due to need for more appropriate care. 5. These individuals will be highly encouraged to contact their primary care provider for referral to behavioral health services. If the individual request staff assistance in reaching out to their primary care provider, staff conducting screening will provide Dr. Earlise Ward's and Lucretia Sullivan Wade's contact information. For individuals who do not have health insurance and no primary care provide, Dr. Earlise Ward or Lucretia Sullivan Wade will provide encouragement and support in reaching out to Access Community Health Center – Federally Qualified Health Center and/ Journey Mental Health Centers. These two agencies provide care to individuals without health insurance.

8.2 Vulnerable Populations

Minors, adults with impaired decision-making capacity, pregnant people, and prisoners will not be included in this research. The study will not include non-English speaking populations.

The PHQ-9 will be used for screening for inclusion and exclusion. PHQ-9 scores of 5-9 (mild), 10-14 (moderate), 15-19 (moderately severe) and 20-27 (severe) represent thresholds. Individuals who screen severe with a score of 20-27 and/or score ≥1 on the suicidal question (question 9) in the PHQ-9 will be excluded. If participants score ≥1 on the suicidal question (question 9), the research staff conducting screening will follow the UWHealth Suicide Risk Evaluation For an Ambulatory Patient Who Has Expressed Suicidal Thoughts Protocol (Appendix B).

8.3 Lifestyle Considerations

Not applicable.

8.4 Subject Identification and Recruitment

A total of 30 subjects will be recruited from one site in the United States, UW-Madison. Individuals from populations who are underrepresented in clinical research (e.g., racial and ethnic minorities, women, individuals from rural/frontier communities, older individuals) will be enrolled with a goal of ensuring that all eligible patients are given the opportunity to participate in novel clinical trials and that research findings can be generalizable to the entire population.

Study participants will be recruited from the SHOW [17] recruitment registry and from the clinical practice at UWCCC clinics.

- SHOW is a shared resource of UWCCC and provides research support and infrastructure with a statewide representative cohort who have provided consent to contact about future unspecified research

and to external data linkages, such as the Wisconsin Cancer Reporting System. The HNC survivors in the SHOW cohort will be informed of the current project and will be invited to participate by the SHOW research team.

- HNC survivors recruited from the UWCCC clinical practice may be identified during routine visits to their oncology care team for HNC treatment and or follow-up. A member of the clinical team will inform potential subjects of the research opportunity and provide an IRB-approved study brochure and invitation letter.
- As the University of Wisconsin-Madison, allows campus-affiliated researchers to use email to send its faculty, staff, and students information about research subject participation opportunities, the research team will share study information via the Department of Information Technology's Engagement Solutions' Research Email Service in addition to the methods described above. We will send these advertisements every 2 weeks, up to 3 times.

8.5 Remuneration

HNC patients and survivors participating in the pilot study will be compensated $25 following baseline data collection; $25 following the end data collection 3 months later. A random subsample of 10 - 15 participants will be randomly selected to participate in a qualitative interview to inform about their experience and satisfaction with IONA Mind, and they will be compensated $50.

8.6 Early Termination and Withdrawal

Subjects are free to withdraw from participation in the study at any time upon request.

The Principal Investigator (PI) may discontinue or withdraw a subject from the study for the following reasons at his/her discretion:

- Subject non-compliance with study requirements (e.g., study intervention non-compliance)
- If any clinical adverse event (AE) or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the subject
- If the subject is no longer an appropriate candidate for participation

Subjects who sign the informed consent form but do not receive the study intervention will be replaced. Subjects who sign the informed consent form and download the IONA Mind app onto their device of preference and then subsequently withdraw, or are withdrawn or discontinued from the study, will be replaced. All individuals who withdraw from the study will have the access to the IONA Mind app disabled.

The research team will document the date of participant withdrawal including discussion of protocol-required safety and/or follow up procedures and subject's intent to complete further study procedures. The research team will attempt to contact the participant and reassume data collection with patient-reported outcome (PRO) submission and counsel the subject on the importance of maintaining PRO submission as 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 with up to 3 telephone calls. These contact attempts shall be documented in the study file Recruitment and Retention Tracking Tool.

If the participant continues to be unreachable, they will be considered to have withdrawn from the study with a primary reason of lost to follow-up. The withdrawn date is the last day of attempted contact.

The study team will attempt to obtain the reasons for withdrawal from subjects in case of early termination or withdrawal.

New participants will be invited to fill a vacant position in the study. PRO collected until withdrawal will be included in data analysis.

9.0 STUDY INTERVENTION

9.1 IONA Mind App

IONA Mind is a digital app that delivers mental health support. For the general public, once users sign up and respond to the initial assessment with PHQ-9 questionnaire, it reaches out to users proactively to offer support, personalized wellbeing plans, and guidance. The tool is available 24 hours, 7 days a week.

For our study, HNC patients and survivors enrolled will receive an access code and be oriented to download and utilize the redesigned IONA Mind app for a 6-week period. The redesign of the application is described in the next section. During the 6-week period of app utilization, enrolled subjects will submit self-reported generated data using the PHQ-9 questionnaires once a week through UW REDCap. No patients' outcomes data will be collected or stored in the app. Following the 6-weeks period, over the course of 1-2 weeks, study participants will receive the SUS satisfaction questionnaire through UW REDCap. In addition, a random sample of 10 - 15 participants will be invited for a qualitative interview about app satisfaction and acceptability. Final follow-up assessment with PHQ-9 for all participants will occur at 1- and 3-month following the completion of app utilization.

9.2 Adaptation of IONA Mind App for HNC

Prior to conducting the pilot study, the research team will iteratively adapt the IONA Mind app to provide psychological support for HNC patients and survivors. They will do this with the input and counsel from people (Head and Neck Patient Advocate Group) who are intimately familiar with the experience of living through HNC, i.e., HNC survivors.

The UW Head and Neck Cancer SPORE has a Patients Advocate Group, whose mission includes offering feedback on research of SPORE investigators, building community between researchers and patients, and providing input on communication with patients. Three members from the SPORE Patients Advocate group who are HNC survivors will self-select to convene the UWCCC HNC Survivors Advisory Board and iteratively redesign the IONA Mind digital application. Each participant will receive $350 in compensation for the time spent reviewing and adapting the IONA Mind materials for HNC patients and survivors' needs.

For the adaptation of IONA Mind, the research team will work with the UWCCC HNC Survivors Advisory Board to identify key aspects of the HNC survivors' journey from diagnosis to the survivorship phase. This will be done using a focus group approach with in-person and virtual weekly meetings. The research team will not systematically collect data from the UWCCC HNC Patient Advocate Group members for data analysis, although aggregate demographic data will be utilized to describe the profile of the team who redesigned the digital app. The key aspects will be prioritized and considered to iteratively redesign the IONA Mind digital app to better support HNC patients and survivors. The research team will then work with the IONA Mind app builders to incorporate changes based on the UWCCC HNC Patient Advocate Group input. The app will be redesigned and adapted until the UWCCC HNC Patient Advocate Group members agree it is adequate to support HNC patients and survivors.

It is estimated that it will take approximately three to six months to come up with that iteration of IONA Mind that will be used in the study.

A sample of the IONA Mind app chatbot responses is presented in the Appendix C.

9.3 Study Intervention Compliance

Consistent implementation of the study protocol will be obtained by assessing the study intervention compliance. All participants enrolled will be carefully scrutinized to ensure compliance with protocol and intervention delivery. This will be done by careful weekly review of data collected on REDCap and in the app by the research team. The study team will review de-identified information about digital app utilization received from IONA Mind© such as number of times the app was accessed, duration of app utilization per day, which modules of the intervention were utilized. No outcome data from participants will be collected in the app.

9.4 Concomitant Therapy

Not applicable.

10.0 STUDY VISITS AND PROCEDURES

10.1 Study Calendar

Study phase	**Screening**	**Baseline**	**IONA Mind utilization**						**Follow-up**				
	Visit 1	Visit 2	Week1	Week2	Week3	Week4	Week5	Week6	Weeks 7-8	Weeks 9-10	Weeks 11-12	Week 13-18	Weeks 19-20
Screening	x												
Review Eligibility	x												
Informed Consent/Assent	x												
Demographics		x											
IONA Mind app utilization			x	x	x	x	x	x					
PHQ-9 PRO data submission on REDCap		x	x	x	x	x	x	x			X[1]		X[1]
SUS data submission on REDCap								x					
Qualitative Interview									X[1]				
Adverse Event Assessment			x	x	x	x	x	x	x	x	x	x	x

[1] The Qualitative interview will occur once during either week 7 or 8. The PHQ-9 PRO will occur once during either week 11 or 12 and again once during either week 19 or 20.

10.2 Screening and Enrollment

The Screening and Enrollment visits and procedures are described in detail below. SHOW, housed in the Department of Population Health Sciences, is a UWCCC shared resource that provides research services across campus to investigators, including project development, access to an existing statewide cohort with consent to contact for research opportunities, study management, recruitment, and conduction, and analytic services. For the current project, SHOW will develop and produce recruitment materials, create and test the data capture instrument in REDCap, enroll participants from the SHOW cohort who meet study criteria, administer the consent process, track participant progress and provide reminder messages, and disperse participant compensation/incentives. After completion of data collection, a SHOW statistician will be responsible for cleaning and analysis of the data under the direction of Dr. Ward and will aid in the interpretation of findings for broader dissemination. The SHOW members participating in this project have the appropriate training and are listed as study team personnel in the MACS IRB application. Although some procedures that occur after initial contact are listed as being done by SHOW, those procedures will be done by personnel who are cross-listed in both SHOW and MACS.

Clinic recruitment (accrual goal n=15): Providers who work with patients and survivors of Head and Neck cancer will be asked to share the study flyer with potentially eligible patients. They will also ask if the patient is interested in learning more about the study and willing to let a study coordinator contact them. If the patient opts to learn more about the study in the clinic, a research coordinator located in the clinic will provide the patient with more information about the study and direct the patient to complete a screening form online, by phone, or in person. The screening form is built on UW SMPH REDCap. Any person who completes the screener will receive the screener follow-up email, which will inform them if they are eligible and the next steps. Patients who are determined to be eligible in the clinic will be offered the informed consent process in person, online, or by phone. Participants will be offered the option to sign the informed consent form utilizing DocuSign. Once the informed consent is signed, the research coordinator located in the clinic or from SHOW team will provide patients with the baseline visit questionnaires links. If the patient opts to learn more about the study at a later time, the patient will fill out the Permission to Contact form and the study coordinator in the clinic will direct participants to the SHOW team. The study coordinator from SHOW team would call (2x) and email (2x) the interested individual and follow the process described below for participants recruited from the SHOW cohort.

SHOW recruitment (accrual goal n=15): The study team will also recruit past participants of the SHOW study (IRB Protocol #2013-0251) who have consented to be contacted about future research study opportunities. Potentially eligible SHOW participants will receive study invitations from the study team via email (2x), mail (2x) and phone call (2x).

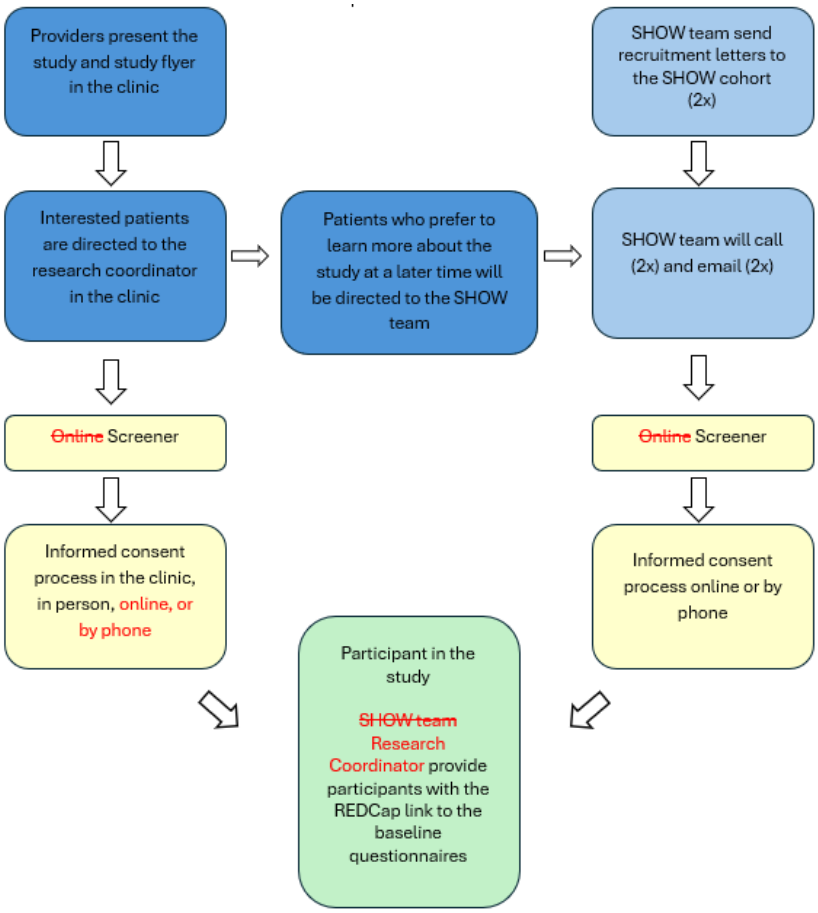
All interested Individuals: would be directed to complete a screening form. Any person who completes the screener will receive the screener follow-up email, which will tell them if they are eligible and the next steps (if eligible), to expect a call from the study team. If a person indicates the idea of self-harm in the online screener, the screener follow-up email will solicit to provide contact information, inform to expect a call from the study team, and provide information about the 988 Suicide & Crisis Lifeline (http://988lifeline.org), a 24-hour, toll-free, confidential suicide prevention hotline available to anyone in suicidal crisis or emotional distress.

During the post-screening phone call, the study coordinator from SHOW will provide an overview of the study and the consent form. During the call, the coordinator will also schedule the baseline appointment with the participant.

After the call, the study coordinator will send the participant an electronic version of the consent form for their review and signature. During the baseline appointment, the coordinator will complete the informed consent process and address any questions the participant may have. Participants will be offered the option to sign the informed consent form utilizing DocuSign. Once the consent form is signed, the coordinator will share links to the baseline visit questionnaires.

Potential participants with a PHQ-9 score <5 in the online eligibility screening will be asked permission to be contacted by the research team for a new assessment at a later date. We will recontact them at a future clinic appointment. We will screen one more time after the initial screen fail. There is not a specified time in which this needs to occur. We also plan to re-approach patients that have previously screen-failed prior to this change in eligibility. For this group, we will ask a member of the care team to first get permission for us to talk with them again during a clinic visit. The goal of rescreening individuals with PHQ-9 score <5 is to offer another chance of participation as treatment and or concerns may progress.

Screening and Enrollment flowchart



10.2.1 Informed Consent

10.2.2.1 If a patient meets gross eligibility criteria, a member of the clinical team will present the study to potential subjects. For those recruited in the clinic the research coordinator will approach interested patients either in clinic (private room) or via the phone after the visit. For those recruited through SHOW the research coordinator will approach interested subjects via phone call.

10.2.2.2 Once a potential subject has been identified, and eligibility confirmed, the consent process will occur either in person during a clinic visit or over the phone or secure videoconference. If the consent process is conducted over the phone/videoconference, the subject will be provided with a copy of the informed consent prior to conducting the consent discussion by fax, mail, or e-mail (if they have agreed to the use of e-mail). Informed consent will be obtained prior to conducting any study activities. Prior to obtaining the patient's signature, the research coordinator will ask the patient to describe their understanding of the study and will correct any misconceptions.

10.2.2.3 Remote Consenting Process: Participants may be consented remotely (via telephone or secure videoconferencing) but must receive a copy of the consent form in advance of the discussion (e.g., provided in person, via mail, fax, email, or DocuSign*). The research coordinator will implement a method to ensure the identity of the participant (e.g., verification of state identification or other identifying documents or use of personal questions such as date of birth or spell first and last name). The research coordinator will explain the study and answer any questions. If the patient agrees to participate, they must sign and date the consent form and return it to the research coordinator via email using a scanner or taking a picture of each page or using DocuSign (as described in the paragraph below).

- DocuSign* Method: If DocuSign is used, the patient can elect to receive the consent via email and follow the secure link to the DocuSign website to review (or print) the consent and electronically sign. The consent which is emailed to the patient will be available to them 24 hours / 7 days a week. The study team will be notified once this has happened. The study team will then counter sign the consent electronically via DocuSign and each party will automatically receive a fully executed copy for their records. All documents will be sent using Part 11 compliant DocuSign.

10.2.2.4 Process to Document Consent in Writing:

- If the patient agrees to participate in the study, the consent form will be signed and dated by the patient and the research coordinator obtaining consent.
- The research coordinator will document the consent process in the participant's electronic medical record, including the date the consent was signed, for participants who are receiving care through UWCCC.
- The participant will be given a copy of the signed and dated consent form for their personal records. The original signed informed consent will be kept in the participant's research record.

10.2.2 Screening Visit

At the screening visit, potential participants will be asked questions about diagnosis of HNC, previous diagnosis of mental health issue, and current utilization of prescription medicine to treat depression to verify eligibility for the study.

The following demographic data will be collected: age, race, ethnicity, marital status, insurance, educational attainment, income, employment activity and status, retirement.

Potential participants will complete the PHQ-9 . Individuals who do meet criteria on the PHQ-9 will have the IONA Mind app downloaded onto the device of their preference (usually a smartphone or tablet) and will receive a brochure with IONA Mind instructions. Individuals who decline to participate or who have scores < 5 or ≥ 20 on the PHQ-9 will not have screening data retained.

Individuals who screen with no or minimal depression scores 0-4 and individuals who screen with severe depression with a score of 20-27 will be informed that they are not eligible for the study due to the level of symptoms. These individuals will be highly encouraged to contact their primary care provider for referral to behavioral health services. If the individual request staff assistance in reaching

out to their primary care provider, staff conducting screening will provide Dr. Earlise Ward's and Lucretia Sullivan Wade's contact information.

Participants who express thoughts that "they would be better off dead or of hurting themselves in some way" characterized by score 1 – 3 on PHQ-9 question 9 during screening visit, will be excluded from participating in the study. The research staff conducting screening will follow the UWHealth Suicide Risk Evaluation For an Ambulatory Patient Who Has Expressed Suicidal Thoughts Protocol (Appendix B).

10.2.3 Baseline Visit

Baseline visit will include documentation of baseline medical history, Activities of Daily Living (ADL), completion of PHQ-9, Work and Social Adjustment Scale (WSAS) , and NCCN Distress Thermometer on REDCap.

Data elements assessed from medical history include:

Cancer diagnosis with ICD 10
Cancer stage

Treatment intent (curative or palliative)
Treatment Modalities (chemotherapy, radiation therapy, surgery)
Income
Employment
Marital Status
Network index
Religiosity

10.2.4 Enrollment

A research subject will be defined as "enrolled" in the study when they meet the following criteria:

- The subject has been consented by study staff.
- The subject and study staff have completed all screening documentation.
- The PI has verified that the subject meets all of the inclusion criteria.
- The PI has verified that subject meets none of the exclusion criteria.
- The subject has been assigned to the protocol by study staff.
- The subject has scheduled a study visit.
- The IONA Mind app has been downloaded onto the participant's device of preference.

10.2.5 Screen Failure and Re-enrollment

Individuals who do not meet the criteria for participation in this trial (screen failure x 2) before providing signed consent will have their data destroyed. We will collect the reasons for ineligibility without identifiers. If the subject is determined to be ineligible after signing consent, we will collect and store the reasons for ineligibility.

10.3 On-Study/Follow-up Visits

After subjects have been enrolled, the On-Study/Follow-up visits and the procedures and evaluations performed at each visit are described in detail below.

Intervention Period - Weeks 1-6

- IONA Mind Utilization program
- PHQ-9 to be completed weekly on REDCap by participant when prompted by IONA Mind app

Week 6

- SUS (satisfaction) data submission on REDCap

Follow-up – Week 7 (+1 week window)

- Qualitative interview over the phone or videoconference with UW HIPAA approved platform (acceptability)

A subsample of 10 –15 participants will be invited to participate in a qualitative interview. The interviews will be recorded to facilitate data analysis.

Minimum allowable time for the qualitative interview: week 7.

Maximum allowable time for the qualitative interview: week 8.

Follow-up – Week 11 (1 month post program)(+1 week window)

- PHQ-9 PRO data submission on REDCap

Participants will complete one assessment prompted by the SHOW team 1 month following the end of app utilization.

Minimum allowable time for 1-month follow-up: week 11.

Maximum allowable time for 1-month follow-up: week 12.

Weeks 1-6 and Follow-up for 3 months

- AE Assessment with PHQ-9 scores weekly review

Final Study Visit- Weeks 19-20 (3-months post program)

Participants will complete one final assessment prompted by the SHOW team 3 months following the end of app utilization.

- PHQ-9 PRO data submission on REDCap
- NCCN Distress Thermometer assessment data submission on REDCap
- Work and Social Adjustment Scale (WSAS) data submission on REDCap

Minimum allowable time for the final study visit: week 19.

Maximum allowable time for the final study visit: week 20.

10.4 At the end of the 6 weeks intervention (app utilization) participant's app study access code will be canceled preventing them from accessing LiCBT materials and interacting with the

app. Follow-up data collection reminders will be sent via email.Early Termination/Withdrawal Visit

Subjects who are either withdrawn or self-terminated early from the study will have adverse events assessed by the research team. The research team will revise the data submitted through REDCap until withdrawal date. Lack of data submission, increasing in depression scores, and suicidal ideation will trigger further assessment as described below (Section 10.6 Procedures and Assessments).

10.5 Long-Term Follow-up | Re-contacting Subjects

Not applicable.

10.6 Procedures and Assessments

10.6.1 PHQ-9: Depression Assessments

The PHQ-9 is a diagnostic tool introduced in 2001 to screen adult patients in a primary care setting for the presence and severity of depression. It rates depression based on the self-administered Patient Health Questionnaire (PHQ). The PHQ is part of Pfizer's larger suite of trademarked products, called the Primary Care Evaluation of Mental Disorders (PRIME-MD). The PHQ-9 takes less than 3 minutes to complete and simply scores each of the 9 DSM-IV criteria for depression based on the mood module from the original PRIME-MD. Primary care providers frequently use the PHQ-9 to screen for depression in patients. PHQ-9 scores of 5, 10, 15 and 20 represent thresholds of mild, moderate, moderately severe, and severe depressive symptoms, respectively.

For PHQ-9, a 5-point change is considered clinically significant, with a score dropping below 10 indicating a partial response, and a score dropping below 5 representing remission.[19]

10.6.2 SUS

SUS[20] (Satisfaction Assessment Questionnaire) has 10 items. Each item is rated on a 5-point scale.

10.6.3 Qualitative Interview

The qualitative interview will be semi-structured with questions to query about experiences and satisfaction with the app. The interview will take 30 – 45 minutes.

10.6.4 AE Assessment

Adverse Effects will be assessed by the research team lead by Dr. Ward, LP, that will weekly evaluate PHQ-9 scores. Lack of data submission will trigger a follow-up phone call to assess reasons for not submitting the data and concerns with app utilization. Increase in depression scores above moderately severe on the PHQ (score ≥19) characterize worsening in depression and will trigger further assessment and referral for appropriate treatment. Suicidal ideation with a score of ≥1 on question 9 on the PHQ-9 will be assessed according to the protocol for suicide risk assessment (Appendix B).

11.0 DATA HANDLING AND RECORD KEEPING

11.1 Data Collection

11.1.1 Data Collection Forms

Standardized data collection forms (e.g., source documents, case report forms, standardized assessment forms, etc. are used to ensure data collected are consistent and compliant with the protocol and IRB application.

Data collection is the responsibility of study team members under the supervision of the Principal Investigator (PI). The PI is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the recorded and reported data.

All data collection forms must be completed in a legible manner; any missing data will be explained. Data entry errors will be corrected with a single line through the incorrect entry and the correct data is entered above/near the correction. All changes will be initialed and dated.

Data collection forms are maintained in the subject files and retained as described in Section 11.3: Records Retention.

11.1.2 Data Management Software System(s)

Clinical data (including AEs and solicited events data) will be entered into the following data management software system(s) to ensure consistent data entry and data quality. Clinical data will be entered directly from the source documents.

OnCore
The Online Collaborative Research Environment (OnCore) Clinical Trial Management Software (CTMS) will be used for this study.

OnCore is a web-based data management system that: a) ensures secure, easy data entry at multiple sites; b) integrates multiple data sources; c) provides controlled, secure access to sensitive data using role-based access control; d) provides workflow automation; and e) allows export and reporting of data for Data (and Safety) Monitoring Committee(s). This software provides protocol and subject management functions (e.g., subject scheduling; screening; data organization), maintains updated forms, addresses budget development, billing and fiscal management, generates summary reports, and provides essential links with research administration and electronic medical records systems. For this project the system will be utilized to register participants' identifying information (name, medical record number, sex, race, ethnicity) and status on study, that will be entered in the UWCCC OnCore database for purposes of monitoring. The OnCore system eases the burden of the individual researcher and unifies protocol management within research programs and across research sites, enhancing protocol integrity and regulatory compliance efforts.

REDCap
The ICTR Research Electronic Data Capture (REDCap) system is used to capture and manage the data for this study.

REDCap is a largely self-service, secure, web-based application for building and managing data collection forms. REDCap provides data management functionality by allowing the development of instruments and surveys to support data capture for research studies.

11.2 Confidentiality and Privacy

Subject confidentiality and privacy are strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their agents. This confidentiality is extended to cover clinical information relating to subjects. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

All research activities will be conducted in as private a setting as possible.

All study staff engaged in the conduct of this project have completed training on the protection of human subjects and the Health Insurance Portability and Accountability (HIPAA) Privacy Rule. In addition, all key

personnel (i.e., Principal Investigator, individuals involved in identifying/recruiting subjects, obtaining informed consent, or interacting and intervening with subjects) have undergone Good Clinical Practice (GCP) training.

Information about study subjects will be kept confidential and managed according to HIPAA requirements. All subjects will sign a combined informed consent and HIPAA authorization form that includes specific privacy and confidentiality rights. Study data will be maintained per federal, state, and institutional data policies.

The investigator(s) will ensure that the identities of subjects are protected by using coded subject information. The log of subject identifying information that links subjects to their study-specific identification number will be maintained by the investigator. The log of subject identifying information will be stored separately from subjects' demographic and outcomes. The log and all study records will be maintained in locked rooms and access will be limited to essential study personnel. Electronic study records/files will be stored on a department server and accessed via networked computers that are password-protected with access provided only to authorized study personnel.

The PI will be responsible for data management and quality control. In addition, we plan to utilize the University of Wisconsin-Madison Institute for Clinical and Translational Research (UW ICTR) Data Monitoring Committee (DMC) to oversee the study specific to data management and quality control.

Data will be in the form of responses to structured interviews and self-report questionnaires about depression, and demographic information. These data will be coded with research ID numbers that are matched to participant identifiers on only a single, non-duplicated master list. This master list will be retained in a locked file in a locked file room. Only the PI will have keys to this file, and only the project staff will have a key to the file room. The PI will review collected data weekly to assure that all informed consent procedures are being followed, that all participant identifiers are removed from all collected questionnaires, and that all files are locked and secured. Data entered into computer files will have only research ID numbers included, and no participant identifiers will be entered into digital format on REDCap. The OnCore system will be utilized for protocol management. Upon completion of the study, the master list of participant names and links to specific research ID numbers will be destroyed, and no link between identifiers and research ID numbers will remain.

Subjects' data will be shared between the UW study team and the IONA Mind© app developers through secure box folder. Data sent from UW to IONA team include subjects' email addresses, and app access codes connected with individual UW REDCap survey links. The goal of sharing subjects' email addresses with app developers is allowing them to send reminders to participants once a week via in-app notification and email. The survey links will be used in in-app dialog and will direct participants to the UW REDCap surveys. Data sent from IONA to UW team include app access codes connected with de-identified app utilization metrics (number of times the app was accessed, duration of app utilization per day, which modules of the intervention were utilized).

From	**To**	**Data Shared**
UW team	IONA Mind team	Subjects' email addresses Individual UW REDCap survey links
IONA Mind team	UW team	App access code Metrics of app utilization

The IONA Mind team will not have access to subjects' survey responses at any time. If an external source clicks on a survey link the possible outcomes are listed below.

Subjects' survey response	**UW REDCap survey view**
Survey not started	Untouched survey
Partially completed survey	*You have partially completed this survey. You have not completed the entire survey, and your responses are thus considered only partially complete. For security reasons, you will not be allowed to continue taking the survey from the place where you stopped. So you have the option to 1) leave your survey responses unchanged as they are, or 2) you may start the survey over from the beginning so that you may complete it (this will delete all your previously existing responses when you begin again). To start the survey again, click the button below. (Start Over Button)*
Completed survey	*Thank you for taking the survey. Have a nice day!*

All materials and data will be kept in the firewall-protected network in the UW School of Medicine and Public Health. Additionally, any hard copy documents will be stored in a locked file cabinet in the UW School Medicine and Public Health. No one other than the investigator and the research staff will have access to the data. When participants complete the initial screening instruments, they will be assigned an ID number, and all subsequent questionnaires completed by the participants on REDCap will be labeled with and linked to their individual ID numbers. Once data has been entered on the computer, only ID numbers (not names) will be associated with individuals' responses to the questionnaires.

If needed, only study team members with authorized access to the electronic medical records (EHR) from UW Health will access participant's data on HealthLink for study purposes, once allowed by the legal medical record holder.

Similar procedures for protecting data confidentiality have successfully been in place for previous studies. No violation of data confidentiality has been discovered through our monitoring procedures.
Authorized representatives of the following groups may need to review this research as part of their responsibilities to protect research subjects: representatives of the IRB, DSMB/DMC, regulatory agencies, and federal oversight agencies. The clinical study site will permit access to such records.

Study staff may use e-mail and/or the postal services to communicate with research subjects, and research subjects may use e-mail and/or the postal services to communicate with study staff, if the subject has agreed to using email in the Informed Consent form. Study staff will inquire about participants preferences. All emails to subjects will be sent from secure institution-based accounts; personal, home or Gmail email accounts will not be used.

To further protect the privacy of study subjects, a Certificate of Confidentiality will be issued by the NIH. This certificate protects identifiable research information from forced disclosure. It allows the investigator and others who have access to research records to refuse to disclose identifying information on research participation in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level. By protecting researchers and institutions from being compelled to disclose information that would identify research subjects, Certificates of Confidentiality help achieve the research objectives and promote participation in studies by helping to assure confidentiality and privacy to subjects.

11.3 Records Retention

It is the investigator's responsibility to retain study essential documents for a minimum period of 7 years following completion of the study per UW-Madison institutional policy, or at least 2 years after the last approval of a marketing application in their country and until there are no pending or contemplated marketing applications in their country or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product, whichever comes last.

11.4 Retention for Future Research: [Optional or Mandatory] Data, Image, Audio- or Video-Recording & Biospecimen Banking

Data will be stored in UW REDCap for up to seven years, and include de-identified patient disease-related information, reported outcomes, and app utilization metrics:

Cancer diagnosis with ICD 10
Cancer stage
Treatment intent (curative or palliative)
Treatment Modalities (chemotherapy, radiation therapy, surgery)
Income
Employment
Marital Status
Network index
Religiosity
PHQ-9 PRO data submitted on REDCap
NCCN Distress Thermometer assessed on REDCap
Work and Social Adjustment Scale (WSAS) data submitted on REDCap
SUS (satisfaction) data submitted on REDCap
Number of times the app was accessed
Duration of app utilization per day
Modules of the intervention utilized

The data will be accessed or made available upon request to the PI, who will evaluate each request individually. Data entering in a NIH data repository will be informed at a later time, before deposition. The consent form informs participants their data will be stored indefinitely due to NIH data repository deposition.

11.5 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol or investigational plan requirements. The noncompliance may be either on the part of the subject, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

It is the responsibility of the Principal Investigator/site investigator/study staff to use continuous vigilance to identify and report deviations. The Principal Investigator is responsible for assessing whether the deviation

constitutes noncompliance as defined by the reviewing IRB and if so, reporting it within the required time frame(s).

11.6 Publication and Data Sharing Policies

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 (https://www.ncbi.nlm.nih.gov/pmc/) 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.

Aggregate results of the study will be shared with the HNC Survivors Advisory Board and participants. If requested, individual results will be shared with participants individually, respecting confidentiality.

12.0 STUDY ANALYSIS

12.1 Sample Size Considerations

The study team aims to determine preliminary efficacy of the intervention to treat depression, assess subjects' satisfaction, acceptability, and engagement with the app. This is a pilot work that does not require power calculation. Literature recommends up to 30 participants for pilot feasibility qualitative work, and a sample of at least 30 subjects per group for quantitative pilot research.[21] In this study we will compare PHQ-9 scores pre and post intervention in sample of 30 participants.

12.2 Subject Population(s) for Analysis

- To test feasibility of the IONA mind app: all subjects who downloaded the IONA Mind app onto their device of preference will be included in the analysis.
- To test preliminary efficacy of IONA Mind app: all subjects who downloaded the IONA Mind app onto their device of preference and completed PHQ-9 questionnaires, will be included in the analysis.
- To test satisfaction and acceptability of the IONA Mind app: all subjects who downloaded the IONA Mind app onto their device of preference and completed the study, including the SUS questionnaire with or without a qualitative interview, will be included in the analysis.

12.3 Statistical Methods

Primary Objective: To adapt the IONA Mind app to be tailored for depression in HNC patients and survivors. Statistical analysis not applicable.

Primary Objective: To identify feasibility of the IONA Mind app tailored for depression comorbid with HNC in HNC patients and survivors. Feasibility of IONA Mind app utilization will be assessed by our Recruitment and Retention Tracking tool that documents the number of individuals screened, recruited, dropped out (and reasons for), refused, and not eligible for the study, and duration of IONA Mind app utilization.

Primary Objective: To determine preliminary efficacy of the IONA Mind app tailored for depression comorbid with HNC in HNC patients and survivors in reducing levels of depression. We will

summarize patient demographic information using counts and frequencies for categorical variables and mean plus standard deviation for continuous variables. We will use a Fisher's exact test to examine differences. Pre- and post-mean changes will be analyzed using the paired Wilcoxon sign rank test with Cohen's D effect sizes. To test the hypotheses that the utilization of the IONA Mind app will reduce levels symptoms of depression, we propose a linear mixed model with random effects specified. Predictive margins and margins plots will be used to graphically display the impact of IONA Mind app on levels of depression. Missing data will be addressed using a case-wise analysis for binary outcomes or last observation carried forward (LOCF). Continuous outcomes with missing data points may also be corrected using a multiple imputation model depending on the type of missingness. We will conduct all analyses using SAS version 9.4.

Primary Objective: To determine satisfaction and acceptability of the IONA Mind app tailored for depression comorbid with HNC in HNC patients and survivors. Data regarding users' satisfaction gathered with SUS questionnaire will be analyzed using descriptive statistics. Qualitative data will be analyzed with dimensional analysis. The analysis processes will be guided by the dimensional analysis method of Schatzman[22] and Kools, McCarthy, Durham, and Robrecht.[23] In using dimensional analysis the key process is to construct and understand the dimensions and processes of a social phenomenon from the subject's perspective. In the present study the phenomenon of study is depression among HNC patients and survivors, and IONA Mind app. Line-by-line analysis of each transcript will be conducted by the research team with the goal of discovering and describing dimensions and processes participants believe are critical in the intervention and their lived experiences with depression comorbid with HNC.

12.4 Planned Interim Analysis

Due to the pilot nature of the study, an interim analysis will not be performed.

13.0 RISK/BENEFIT ASSESSMENT

13.1 Known Potential Benefits to the Subjects

If this study is able to show a therapeutic benefit of the IONA Mind app in treating depression comorbid with HNC, participants in the intervention will benefit from a decrease in depression symptoms, which has the potential to improve mental health outcomes. In addition, if results are positive, it will benefit others through dissemination to inform evidence-based care implementation and scalability as well as inform possibilities for future research.

13.2 Known Potential Risks

Potential risks include a) emotional reaction to being asked about depression due to the stigma associated with mental illness among HNC survivors; and b) suicidal ideation which is a symptom of severe depression. All research staff will be trained to appropriately manage participant emotional response and provide participants with a debriefing session if they have a strong emotional reaction during app utilization and or data collection. Research staff will be trained by Dr. Ward (licensed psychologist) to manage adverse reactions (suicidal ideations) participants may experience while in the study and the intervention. In addition, a protocol will be in place for the clinicians, research assistants, research coordinator, and project manager to follow if any of the participants develop suicidal ideations during the course of the trial, which will include following the UWHealth Suicide Risk Evaluation For an Ambulatory Patient Who Has Expressed Suicidal Thoughts. Dr. Ward will be contacted immediately to facilitate immediate referral for appropriate care. The PI is a licensed psychologist who has extensive experience working with individuals with clinical depression.

In terms of participant safety monitoring, each participant will be given the telephone number of the PI and Research Manager (Lucretia Sullivan-Wade). For contact during work hours (8:00am-5:00pm) research

project information number will also be given to participants. Individuals needing help after work hours for serious illness will be encouraged to call 911 or 988 (National Suicide Crisis Line). Participants will be encouraged to call the PI or Research Manager if they experience significant distress from participating in the project intervention and or assessment components. As in past studies, the PI will personally telephone every participant who indicates they are very distressed. Moreover, the project research staff and treatment providers will be instructed to contact the PI and inform her about any participants who appear significantly distressed by either the intervention and or data collection. All such participants will then be contacted personally by the PI to assure that their distress is not extreme. In cases where the distress is extreme, the PI will decide upon, and provide appropriate referrals to care and resources.

It is important to note if the adverse event involves subject suicidality, staff or PI will follow the UWHealth Suicide Risk Evaluation For an Ambulatory Patient Who Has Expressed Suicidal Thoughts Protocol (Appendix B)and take necessary mediation to get the subject medical care immediately. All study personnel are directed to email/phone/text the PI immediately if any adverse events occur and to send follow-up email message documenting the potential issue and all actions that were taken. The email will contain study ID number only, without any identifying information. A copy of the email message will be placed in the subject's study file in a locked file cabinet in the PI's research office.

HNC adult survivors with clinical depression might be considered a vulnerable population due to the level of disability associated with clinical depression. We have safeguards including our intervention, trained staff (psychologists) and access to federally qualified health centers to support this group.

The risk of a breach of confidentiality is minimized by the intervention delivered via mobile app. The research team will remind participants of the need for confidentiality.

13.3 Risk/Benefit Analysis

Considering the prevalence of depression among HNC patients and survivors and the LiCBT potential to increase access to mental health treatment and outcomes, we believe the potential benefits of the IONA Mind app outweigh the identified risks in light of the steps we are taking to mitigate the risks.

14.0 DATA AND SAFETY MONITORING

14.1 Adverse Event (AE) Definition

An AE is any untoward medical occurrence whether or not considered related to the study device that appears to change in intensity during the course of the study. The following are examples of AEs:

- Unintended or unfavorable sign or symptom
- Worsening of depression levels while participating in the protocol
- An intercurrent illness or injury that impairs the well-being of the subject and prevents the utilization of IONA Mind app

Adverse Events monitored in this research are those that prevent participants from utilizing the app such as lack of data submission, increase in depression scores above severely moderate depression on the PHQ-9 (score ≥ 20), and suicidal ideation will be assessed according to the UWHealth Suicide Risk Evaluation For an Ambulatory Patient Who Has Expressed Suicidal Thoughts Protocol (Appendix B). Participants will be encouraged to contact their providers in case of adverse effects related to cancer, cancer treatment, and management of comorbid conditions other than depression.

Hospitalization for elective surgery or routine clinical procedures that are not the result of an AE (e.g., surgical insertion of central line) should not be recorded as an AE.

Disease progression should not be recorded as an AE.

14.2 Serious Adverse Event (SAE) Definition

An adverse event is considered "serious" if, in the view of either the investigator or sponsor, it meets any of the following outcomes:

- Death
- A life-threatening adverse event
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- Suicide ideation
- Important Medical Events (IME) that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

14.3 Classification of an Adverse Event

14.3.1 Relationship to Study, Study Procedure(s) and/or Study Intervention(s)

For all collected AEs, the clinician who examines and evaluates the subject will determine the AE's causality based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below.

Definitely Related	Clearly related to the study procedures/intervention and other possible contributing factors can be ruled out.
Probably Related	Likely related to the study procedures/intervention and the influence of other factors is unlikely.
Possibly Related	Possibly related to the study procedures/intervention and there are other factors that could be equally likely.
Unlikely to be related	Doubtfully related to the study procedures/intervention and there is another likely cause.
Unrelated	Clearly not related to the study procedures/intervention and/or evidence exists that the event is definitely related to another cause.

14.3.2 Expectedness for Study, Study Procedure(s) and/or Study Intervention(s)

An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described in the clinical protocol, the IRB application, or the informed consent document. The expectedness could be based on study procedures or the characteristics of the patient population.

14.4 Time Period and Frequency for Event Assessment and Follow-Up

The occurrence of an AE or SAE may come to the attention of study personnel during weekly PRO reviews and interviews of a study subject presenting for medical care, or upon review by a study monitor. AEs that may prevent app utilization will be captured on the appropriate CRF. Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the subject is screened will be considered as baseline and not reported as an AE. However, if the study subject's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The PI will record all reportable events with start dates occurring any time after the IONA Mind app is downloaded to the participant's device of preference and for up to 30 days after the 6-week intervention period. Every week the research team will review the data submitted on REDCap to evaluate the occurrence of AE/SAEs since the last data submission. Events will be followed for outcome information until resolution, stabilization, or completion of study participation.

14.5 Reporting AEs and SAEs

14.5.1 Reporting AEs

- AEs will be recorded any time after the IONA Mind app is downloaded to the participant's device of preference until 30 days after the 6-week intervention period.
- AEs will be recorded regardless of whether or not they are considered related to the study intervention.
- All AEs will be recorded on the appropriate study specific eCRF form within the clinical trial management system (i.e., REDCap).
- The reporting requirements to the IRB and to the sponsor may differ and must be complied with.

14.6 Reporting Serious Adverse Events

14.6.1 SAE – Reported Within 24 hours

Serious Adverse Events requiring reporting within 24 hours (as described in the protocol) must also be reported to the Data and Safety Monitoring Committee (DSMC) Chair, or designee, via an email to *saenotify@uwcarbone.wisc.edu* within one business day. The OnCore SAE Details Report must be submitted along with other report materials as appropriate (NCI AdEERS form or FDA Medwatch Form #3500 and/or any other documentation available at that time of initial reporting). The DSMC Chair, or designee, will review the information and determine if immediate action is required. Within 10 working days, available subsequent SAE documentation must be submitted electronically along with a 24-hour follow-up SAE Details Report and a completed UWCCC SAE Routing Form to *saenotify@uwcarbone.wisc.edu*. Information is entered and tracked in the UWCCC database.

The Principal Investigator notifies investigators involved with the study at the UWCCC, the IRB, the sponsor, and the funding agency and provides documentation of these notifications to the DSMC.

See Section 14.7 Expedited Reporting of Serious Adverse Events for detailed instructions on SAE reporting.

14.6.2 SAE – Reported Within 10 days

Serious Adverse Events requiring reporting within 10 days (as described in the protocol) must also be reported to the Data and Safety Monitoring Committee (DSMC) Chair, or designee, via an email to *saenotify@uwcarbone.wisc.edu*. The OnCore SAE Details Report must be submitted along with other report materials as appropriate (NCI AdEERS form or FDA Medwatch Form #3500 and/or any other documentation available at the time of initial reporting). The DSMC Chair, or designee, will review the information and determine if further action is required. Information is entered and tracked in the UWCCC database.

The Principal Investigator notifies investigators involved with the study at the UWCCC, the IRB, the sponsor, and the funding agency and provides documentation of these notifications to the DSMC.

See Section 14.7 Expedited Reporting of Serious Adverse Events for detailed instructions on SAE reporting.

14.6.3 Sponsor-Investigator Responsibilities for SAE Review

Not applicable. IONA Mind is a software as a medical device digital therapeutic mobile application. The device is being used to treat depression in head and neck cancer patients who are awaiting, receiving or have undergone cancer treatment and qualify as a non-significant risk device.

14.6.4 Study Progress Review

Protocol Summary Reports (PSR) are required to be submitted to the DSMC in the timeframe determined by the risk level of the study (quarterly, semi-annually, or annually). The PSR provides a cumulative report of SAEs, as well as instances of non-compliance, protocol deviations, and unanticipated problems, toxicities and responses that have occurred on the protocol in the timeframe specified. PSRs for those protocols scheduled for review are reviewed at each DSMC meeting.

Protocol Summary Reports enable DSMC committee members to assess whether significant benefits or risks are occurring that would warrant study suspension or closure. This information is evaluated by the DSMC in conjunction with other reports of quality assurance activities (e.g., reports from Internal Audits, Quality Assurance Reviews) occurring since the prior review of the protocol by the DSMC. Additionally, the DSMC requires the study team to submit external DSMB or DSMC reports, external monitoring findings for industry-sponsored studies, and any other pertinent study-related information.

In the event that there is significant risk warranting study suspension or closure, the DSMC will notify the PI of the DSMC findings and ensure the appropriate action is taken for the protocol (e.g., suspension or closure). The DSMC ensures that the PI reports any temporary or permanent suspension of a clinical trial to the sponsor (e.g., NCI Program Director, Industry Sponsor Medical Monitor, Cooperative Group Study Chair) and other appropriate agencies.

14.7 Expedited Reporting of Serious Adverse Events

Depending on the nature, severity, and attribution of the serious adverse event an SAE report will be phoned in, submitted in writing, or both according to Table 1 below. Serious adverse events must also be reported to the UWCCC Data and Safety Monitoring Committee Chair, or designee. Serious adverse events must also be reported to the UW IRB (if applicable), and any sponsor/funding agency not already included in the list.

Determine the reporting time line for the SAE in question by using the following table. Then refer to sections A and B below if the SAE occurred at the UWCCC.

TABLE 1

Phase 1 and Early Phase 2 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention [1,2]

FDA Reporting Requirements for Serious Adverse Events (21 CRF Part 312)
NOTE: Investigators **MUST** immediately report to the UWCCC DSMC, UWCCC IRB, the IDE-holderand any other parties outlined in the protocol ANY Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64).

An adverse event is considered serious if it results in ANY of the following outcomes:

1) Death.
2) A life-threatening adverse event.
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours.
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria* **MUST** be immediately reported to the UWCCC within the timeframes detailed in the table below:

Hospitalization	Grade 1 and Grade 2 Timeframes	Grade 3-5 Timeframes
Resulting in hospitalization ≥ 24 hrs	10 Calendar Days	24 Hour; 5 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required	

Disease relapse and associated with complication from the disease relapse will not be considered intervention related.

Expedited AE reporting timelines are defined as:

- **24-Hour; 5 Calendar Days** – The AE must initially be reported within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- **10 Calendar Days** – A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE

[1] Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 3, 4, and 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 AEs resulting in hospitalization or prolongation of hospitalization

[2] For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

14.7.1 SAE Requiring 24 Hour Reporting Occurs at UWCCC

14.7.1.1 Report to the UWCCC

Reference the SAE SOP (Standard Operating Procedure) and the SAE Reporting Workflow for DOTs on the UWCCC Clinical Research KB website for specific instructions on how and what to report to the UWCCC for [24] hour initial and follow-up reports. A follow-up report is required to be submitted within 10 days of the initial [24] hour report.

For this protocol, the following UWCCC entities are required to be notified:

a) *saenotify@uwcarbone.wisc.edu*

b) Earlise C. Ward, PhD, LP

c) UWCCC Program Manager

d) Any other appropriate parties listed on the SAE Routing Form (for follow-up reports only)

14.7.1.2 Report to the IRB

Consult the UW Health Sciences IRBs website for reporting guidelines.

14.7.2 SAE Requiring [10] Day Reporting Occurs at UWCCC

14.7.2.1 Report to the UWCCC

Reference the SAE SOP and the SAE Reporting Workflow for DOTs on the UWCCC Clinical Research KB website for specific instructions on how and what to report to the UWCCC for [10] day reports.

For this protocol, the following entities are required to be notified:

a) *saenotify@uwcarbone.wisc.edu*

b) Any appropriate parties listed on SAE Routing Form

14.7.2.2 Report to the IRB

Consult the UW Health Sciences IRBs website for reporting guidelines.

14.7.3 Other Reporting Requirements

The PI will report adverse effects in writing within 48 hours to the NIH program officer.

Following each adverse event, an investigation of the circumstances precipitating the event, all probable factors, the current status of the event, and the outcome of the event will be conducted by the PI. A written summary of findings will be submitted to the NIH Project Officer(s).

14.8 Reporting of Pregnancy

Not applicable.

14.9 Unanticipated Problems

An unanticipated problem (UP), as defined by the DHHS Office for Human Research Protection (OHRP), is any incident, experience, or outcome that meets all of the following criteria:

- The incidence, experience, or outcome is unexpected given the research procedures described in protocol-related documents (e.g., the study protocol, the informed consent documents) and the characteristics of the subject population being studied. An event may be considered unexpected if it

exceeds the nature, severity, or frequency described in the study-related documents or product labeling.
- The incidence, experience, or outcome is related or probably related to participation in the research study. “Probably related” means the incidence, experience, or outcome is more likely than not to be caused by the research study procedures.
- The occurrence of the incidence, experience, or outcome suggests that the research places subjects or others at a greater risk of harm (physical, psychological, economic, or social) than was previously known or recognized.

The investigator will report UPs to the reviewing IRB. 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, informed consent documents, or other corrective actions that have been taken or are proposed in response to the UP.

Report UPs within the timeframe(s) specified by the IRB(s) of record.

14.10 Safety Oversight

14.10.1 Oversight and Monitoring Plan

The UWCCC Data and Safety Monitoring Committee (DSMC) is responsible for the regular review and monitoring of ongoing clinical research in the UWCCC. A summary of DSMC activities are as follows:

- Review clinical trials conducted at the UWCCC for subject safety, protocol compliance, and data integrity.
- Review Serious Adverse Events (SAE) requiring expedited reporting, as defined in the protocol, for clinical trials conducted at the UWCCC, and studies conducted at external sites for which the UWCCC acts as an oversight body.
- Review reports generated through the UWCCC DSMS elements (Internal Audits, Quality Assurance Reviews, Response Reviews, Compliance Reviews, and Protocol Summary Reports).
- Notify the protocol Principal Investigator of DSMC decisions and, if applicable, any requirements for corrective action related to data or safety issues.
- Work in conjunction with the UW Health Sciences IRB in the review of relevant safety information as well as protocol deviations, non-compliance, and unanticipated problems reported by the UWCCC research staff, when appropriate.

14.10.2 Monitoring and Reporting Guidelines

UWCCC quality assurance and monitoring activities are determined by study sponsorship and risk level of the protocol as initially determined by the PRMC. Protocols (including Intervention Trials, Non-Intervention Trials, Behavioral and Nutritional Studies, and trials conducted under a Training Grant) are evaluated by the PRMC at the time of committee review. The DSMC may direct a study team to change the Protocol Summary Report submission frequency during the conduct of the study. UWCCC monitoring requirements for trials without an acceptable external DSMB are as follows:

Intermediate Monitoring: Protocols subject to intermediate monitoring generally include UW Institutional Phase I/II and Phase II Trials. These protocols undergo review of subject safety at regularly scheduled DOT meetings where the results of each subject’s treatment are discussed and the discussion is documented in the DOT meeting minutes. The discussion includes the number of

subjects enrolled, and responses observed. Protocol Summary Reports are submitted on a semi-annual basis, unless directed otherwise by the DSMC, by the study team for review by the DSMC.

14.11 Study Monitoring

This UWCCC single-site institutional clinical trial will be monitored/audited according to the UWCCC DSMP.

14.12 Study Stopping Rules

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 regulatory authorities. If the study is prematurely terminated or suspended, the PI will promptly inform the IRB and will provide the reason(s) for the termination or suspension.

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

- Determination of unexpected, significant, or unacceptable risk to subjects
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination of futility

Study may resume once concerns about safety, protocol compliance, data quality is addressed and satisfy the applicable federal and institutional regulatory authorities.

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16.0 APPENDICES

Appendix A -- Study Timeline

Research activities	**YR1**			
Quarter	1	2	3	4
Digital app adaptation with HNC Survivors Advisory Board				
Recruitment of study participants				
Screening & enrollment				
Start Intervention (IONA Mind digital app utilization for 6 weeks)				

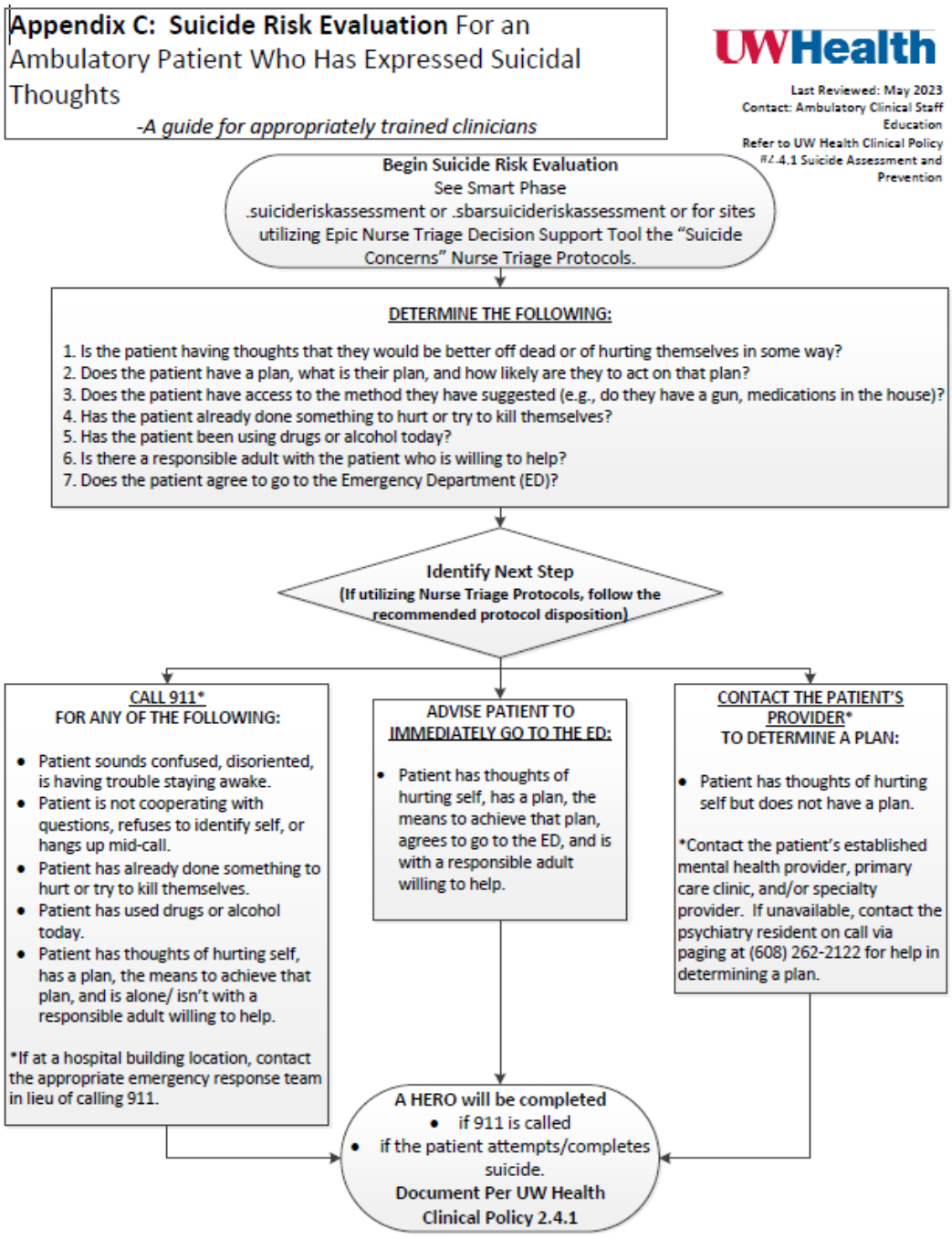
End of intervention				
Follow-up 1- and 3-months post intervention				
Data cleaning				
Analysis				
Grant reports & manuscript preparation				
Dissemination (e.g., manuscripts, community presentations, and national conferences)				

Appendix B -- Suicide Prevention Protocol

Mental Health App for Cancer Survivors Study (MACS Study)

Procedures for Suicide Risk Assessment triggered by PHQ-9 question 9 score 1-3

Research staff at Screening Visit:



Suicide Prevention Protocol for staff training

I. Assess risk factors:

- Increased substance abuse
- Social withdrawal
- Family history of suicide
- Physical Illness
- Single, separated, widowed, divorced

- Unemployment
- Presence of a psychiatric diagnosis, particularly an affective disorder
- Previous suicidal attempts
- Participant threatening to hurt/kill him/herself or wanting to hurt him/herself
- Seeking means (e.g. accessing firearms, pills) to kill him or herself

Although these factors do not predict suicide behavior assessing, can give clinician information for further assessing the severity of possible suidality.

Source: Jacobs, Brewer, & Klein-Benheim (1999)

II. Questions to consider if participant endorses suicidal thoughts:

- What are the thoughts?
- Are they active or passive?
- When did they begin?
- How frequent are they?
- How persistent are they?
- Are they obsessive?
- Can you control them?
- Loss of coping mechanism?
- How far has the suicide process proceeded?
- Have suicidal behaviors occurred in the past?
- Has the participant lost or anticipates losing his/her main reason for living?

Increased frequency, specificity and intensity of thoughts indicate that participant may be suicidal and should not participate in study.

Source: Risk Management Foundation of the Harvard Medical Institutions

III. Protocol for Working with Suicidal Participants

- Inform participants prior to counseling of the limitations of confidentiality (i.e. informing third parties about suicidality)
- If participant is identified as experiencing suicidal ideation, conduct a suicide risk assessment; if positive contact Dr. Ward (608-622-1530) immediately.
- Dr. Ward will work with mental health clinician and the participant to obtain appropriate care.
- When appropriate inform family members of the need to limit the access to any means of suicide and provide supervision.
- Document the incident in incident report.
- Dr.Ward will inform Data Safety Monitoring Committee (DSMC) and IRB.

Appendix C – Sample of chatbot scripted responses and Example of email to study staff in case of dangerous input into the app

DESCRIPTION OF FUNCTION OF APP CHATBOT

The chatbot is used primarily as a delivery tool for CBT lesson content. In general, the user is not allowed to enter freeform text into the chat, but instead chooses from a number of predetermined options. What the chatbot says and what the options are, are fully scripted and deterministic. The chatbot will, for example, never encourage a user to have an abortion, because we have never written this into the script. The content has been carefully scripted and reviewed by psychology experts to ensure it is acceptable and has high fidelity to the core interventions on which it is based.

The chatbot is also used in a supporting function, but again, what the chatbot says is fully and manually scripted based on a set of pre-programmed rules. The supporting function does not differ substantially from lesson content in how it functions.

As part of some of the CBT exercises (e.g. activity scheduling as part of a Behavioral Activation intervention), it may be necessary for the user to enter some free text - for example the activity that they want to schedule. Generally speaking, this input does not normally take place in the “chat” with the chatbot, but instead, in this case, will be into the activity picker which the user uses as part of the calendar and scheduling functionality in the app. There are occasions when the user is required to enter free text into the chat, as part of a structured CBT exercise, such as entering the name of an activity, or a step in an activity. In these cases (as in all cases) input is checked using a number of rules and models to ensure it does not contain references to suicide, substance abuse, physical violence or generally abusive language.

EXAMPLE LESSON SCRIPT (DELIVERED THROUGH CHATBOT)

In this example chat script, options for the users are in square brackets [ ]

Have you ever heard of the term ‘avoidance’ when it comes to your mental health?

[Yes] [No]

{if yes => Good, understanding this is very important because it’s the basis for understanding how increasing your activity levels can improve your mood [Ok]

If no => I'll quickly explain more because it's basis for understanding how increasing your activity levels can improve your mood [Ok]

When feeling low it's common to lack energy and not be interested in doing things you used to enjoy

[I've had that] [Ok]

Doing less can give you a **sense of relief**

You do less and so you feel less tired

[Go on…] [What's the downside?]

🛑 While it's understandable to avoid doing things, the relief it brings can be **unhelpful** 🛑

[Explain how] [Ok]

Once you start not doing things you like or need to do, your mood can drop, and you can get stuck in a **downward spiral**

I recommend a quick 1 minute example to really understand how this can happen. But we can also skip straight to how to break the cycle if you like? You're in control 🙄

[Give example] [Skip it]

Here's an example of a downward spiral of low mood and reduced activity

It's a common example but may not apply to you

[I understand]

Example: It starts with feeling down, tired, having less motivation and negative thoughts

[⬇️] [Skip example]

Next you start avoiding things you like or need to do

[⬇️] [Skip example]

Then you initially feel a bit better. You feel relief from not doing things

[⬇️] [Skip example]

However, as you do less you miss out on things you used to like and your list of things you need to do grows

[⬇️] [Skip example]

As your mood drops even lower you experience greater relief from doing fewer and fewer things

[Makes sense] [Continue] [I've experienced that]

This spiral is common when experiencing low mood so try not to beat yourself up if you find yourself in one

[I'll try] [Ok]

(Skip example ends up here)

One of the most effective and widely used ways to break out of a vicious cycle of low mood and avoidance is to **plan** and **do** activities every day

The idea is to gradually build your activity level back up, breaking you out of the cycle of avoidance

[Makes sense] [Ok]

It's best if you plan the activity beforehand because when you plan up front, you're more likely to follow through and break the vicious cycle

This is what the research shows

[Got it] [I'll try my best]

When you start planning and doing new things you'll feel a **sense of achievement** and accomplishment

This then makes it easier to plan and do more things and creates an **upward spiral** instead of the downward spiral

[Sounds good]

As you've seen in previous lessons, this app is designed to make it easy for you to plan and do activities

[Ok] [Remind me]

Remind me =>

Previously you learned that your thoughts, physical feelings, emotions and behaviors are all related and affect each other

[Ok] [I remember]

That means if you start making a change to one of these areas, it can affect all of the others

In this course you looked at changing your behavior by increasing your activity level

[Ok][I remember]

The way you can increase your activity level is to plan and do activities

[Ok]

The next step is to use the app to plan and track activities every day

Once you've finished an activity, come back and mark it complete so you can track your progress and reflect on how things are going

[Let's do this]

Lesson Summary

Title : Breaking the downward spiral

Subtitle : Build up a sense of achievement

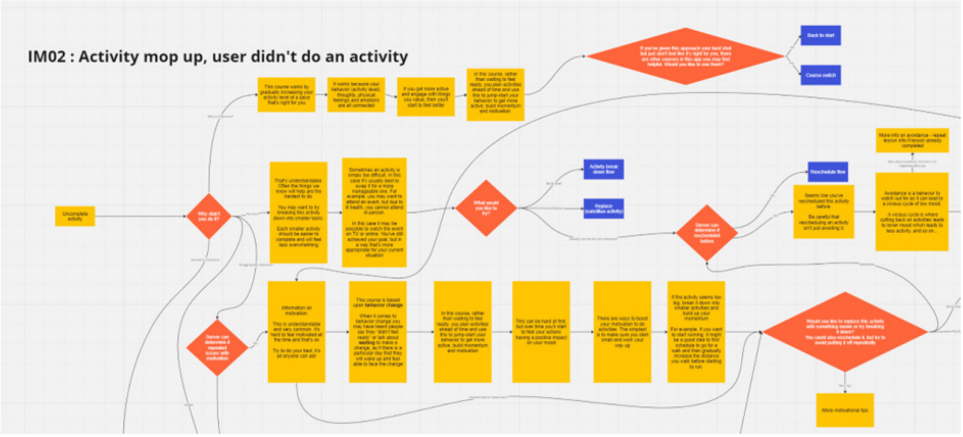
'Avoiding things and doing less can give you a sense of relief',

'Eventually the sense of relief becomes unhelpful as it leads to a vicious cycle of lower mood and less activity,

'Slowly start to build up you activity to break the cycle and improve your mood',

EXAMPLE SUPPORTIVE FLOW

Example part of a flow chart documenting the flow of a conversation when supporting a user who did not complete an activity as part of behavioral activation.



CHECKING USER INPUT

In the cases where the user is allowed to enter free text into the app, regardless of where that free text is entered, the text is checked for the following things:

- **Emergency or crisis**
  These checks relate to words or word sequences that could relate to suicide, death or murder. This is a rules based check based upon word, word fragment and sentence fragment checks.

- **Abusive language**
  These checks relate to the use of general foul language such as profanities and insulting language. This is a part rules based check and partly based on an AI model trained on a database of abusive internet comments.

- **Drugs and substance use**
  Reference to words which could be names or slang terms for illicit substances and sentence fragments that could indicate substance use. This is a rule based check from a database of drug names and other slang terms.

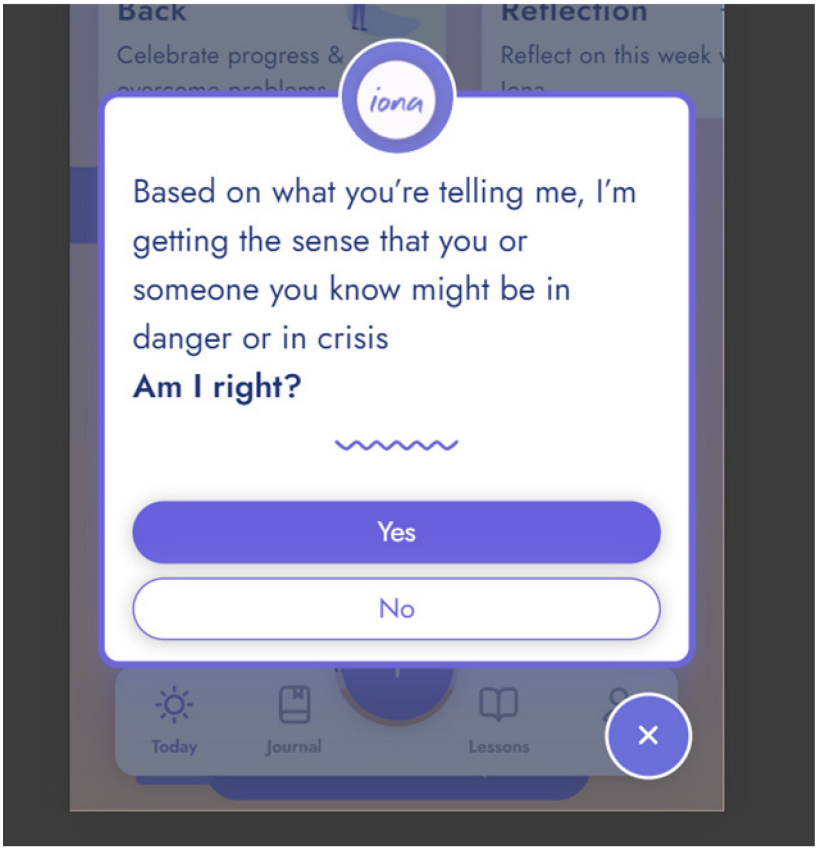
- **Panic attack**
  A rules based check for sentence fragments which might indicate the user is having a panic attack.

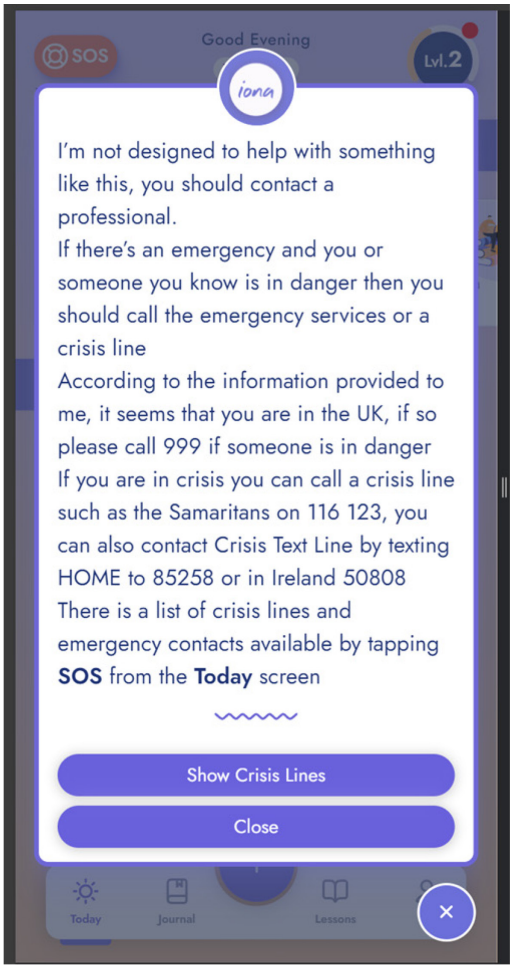
- **Personal abuse**
  These checks relate to words or word sequences that could relate to sexual or physical abuse. This is a rules based check based upon word, word fragment and sentence fragment checks.
  Should any of the above be triggered, they will either trigger a response from the chatbot first asking the user if they or someone they know is in danger (in the case of abuse), if the user answers yes, the user is

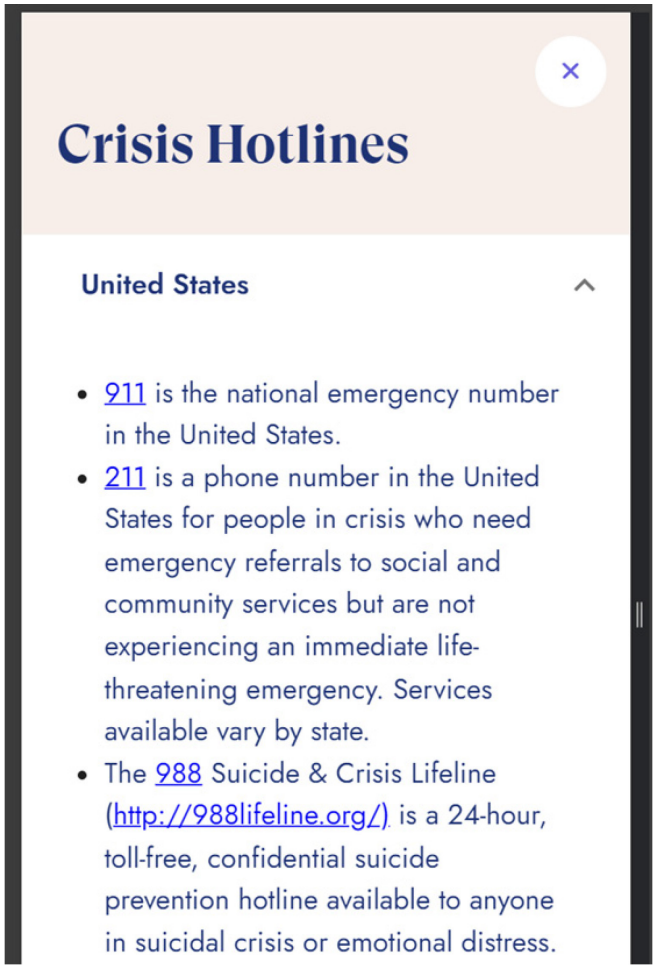
signposted to emergency lines and told that the app is not appropriate for them. If the user answers no, they are still reminded that should that be the case, they should stop using the app and contact emergency services. In addition, an email to study staff is triggered if any of these input checks trigger, regardless of the user's response.

Example responses for dangerous input

These are illustrative only and do not represent the responses generated for US users.



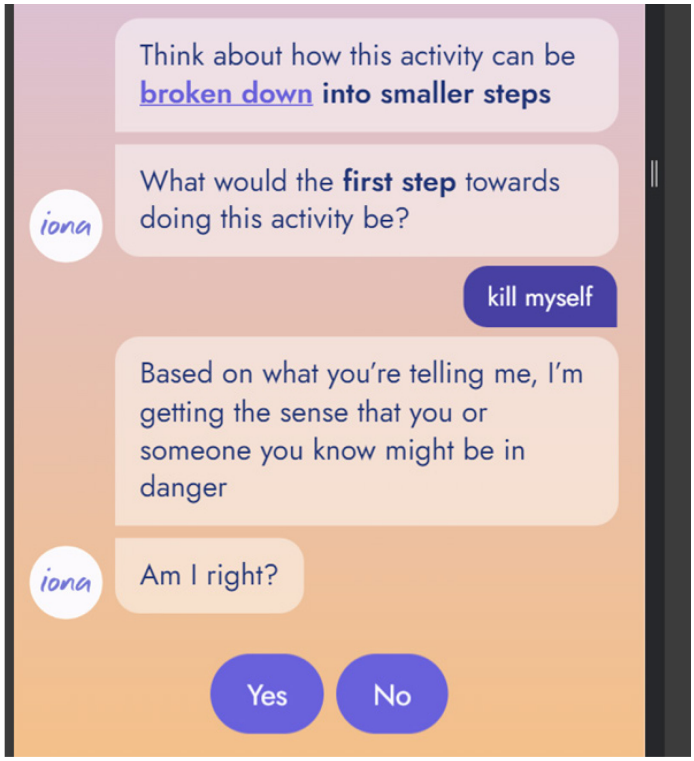

SOS
Good Evening
Lvl.2
iona
I'm not designed to help with something like this, you should contact a professional.
If there's an emergency and you or someone you know is in danger then you should call the emergency services or a crisis line
According to the information provided to me, it seems that you are in the UK, if so please call 999 if someone is in danger
If you are in crisis you can call a crisis line such as the Samaritans on 116 123, you can also contact Crisis Text Line by texting HOME to 85258 or in Ireland 50808
There is a list of crisis lines and emergency contacts available by tapping **SOS** from the **Today** screen
Show Crisis Lines
Close
Today
Journal
Lessons



Crisis Hotlines

United States

- 911 is the national emergency number in the United States.
- 211 is a phone number in the United States for people in crisis who need emergency referrals to social and community services but are not experiencing an immediate life-threatening emergency. Services available vary by state.
- The 988 Suicide & Crisis Lifeline (http://988lifeline.org/) is a 24-hour, toll-free, confidential suicide prevention hotline available to anyone in suicidal crisis or emotional distress.



Example detection

EXAMPLE OF AUTOMATED EMAIL TO STUDY STAFF

In the event of any of the above checks being triggered an automated email is sent to a list of study staff. The email contains the sign up code given by the user during the sign up process, and an indication of which of the checks was triggered and the time of trigger. No further information is provided (including the input). Study staff can relate the sign up code back to a trial participant.

An example of the email template is shown below:

Subject Line

URGENT: Iona App Trial User Alert

Body of email

The Iona App has detected potentially dangerous input from a user.

Trigger time in user's time zone: 2024-03-25 15:34:22

Sign up code: 3301AYZ

Trigger Type: Drugs or Substance Use