INVESTIGATOR STUDY PLAN – Take a Break (H00007427)

1) **Title**

Take a Break (TAB): mHealth-assisted skills building challenge for unmotivated smokers

2) **IRB Review History**

N/A

3) **Objectives**

Take a Break (TAB) is a randomized trial designed to evaluate Nicotine Replacement Therapy (NRT)-sampling and a mHealth suite of apps. TAB is a time-limited self-efficacy and skills building experience for Motivation Phase smokers. TAB is designed to create a timeline within which motivation smokers will be encouraged to try a brief period of abstinence. Smokers in this Motivation Phase are relatively untapped in research available information. This project offers these smokers point-of-need technology support in the many components of the intervention.

Our Specific Aims are

- AIM 1: Refine the Take a Break mHealth tool and implementation program.
- AIM 2: Conduct a randomized trial of the effectiveness of Take a Break.
- AIM 3: Follow participants in the AIM 2 randomized clinical trial for 6 months to evaluate time to quit attempts, number of quit attempts, and 6-month biochemically verified point prevalent cessation.

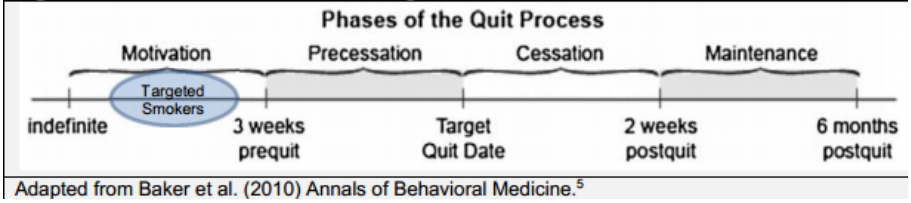
The Take a Break intervention is designed to increase self-efficacy and support new skills for Motivation Phase smokers. We hypothesize that, compared with the NRT-only group, the Take a Break group will have a greater number of days abstinent during the 'break' period, a greater increase in self-efficacy at the end of the 'break' period, a lower time to first quit attempt, and a higher rate of quit at 6 months. This research study will also provide valuable insight into this population of smokers and increase our understanding of which tools may be effective in helping them quit smoking.

4) **Background**

Smoking is the leading preventable cause of mortality in the United States.[1] The use of pharmacological cessation aids combined with behavioral counseling doubles the chances of successfully achieving long-term cessation.[2] However, the majority (70-90%) of smokers are not actively quitting at any given time.[3] In smoking cessation research, the majority of evidence applies to the minority of smokers, those actively quitting. This known gap is significant because the majority of smokers–those who are not ready to quit smoking, also described as smokers in the "Motivation Phase" of the Phased Framework of Smoking Cessation, historically, have not been the focus of cessation interventions. In the Phased Framework of smoking cessation interventions,[4] smokers can be considered in several phases (Figure 1). In Take a Break, we are focused on Motivation Phase smokers.[4,5] Although some smokers are not willing to quit, many of these smokers are thinking of quitting in the future, but may need additional support and motivational interventions.

Engaging those not ready to quit in treatment is challenging. However, prior interventions have been successful in engaging up to

Figure 1: Phased Framework of smoking cessation interventions



Adapted from Baker et al. (2010) Annals of Behavioral Medicine.[5]

half of smokers who refuse cessation treatment in a brief, non-cessation experience.[3,6] Precessation NRT can increase subsequent quit rates. In a meta-analysis, nicotine therapy (NRT) was estimated to double six-month cessation in Motivation Phase smokers.[7] Effectiveness data from these studies[8-10] demonstrates the potential of NRT-sampling in these smokers.

As noted in a recent review,[5] "One opportunity in the Motivation Phase is that there is time for smokers to learn and practice skills before undergoing cessation-related withdrawal." In Motivation Phase interventions, the goal has been to increase a smoker's confidence and skills related to smoking cessation. Motivation Phase smokers are asked to reflect upon smoking, briefly practice behaviors used during quitting, and develop new skills for managing smoking urges. Conceptually, these goals and strategies are related to core constructs from the Social Cognitive Theory including self-efficacy.[11] Self-efficacy has been defined as the perceived capacity to perform a behavior.[12,13] Self-efficacy can influence outcome expectations. Our game is designed to enhance self-efficacy in the context of brief abstinence, and subsequently in quit attempts. Self-efficacy can influence other factors including outcome expectations that influence goalsetting.[14] In Take a Break, we will encourage participants to set goals for the brief abstinence Marathon, and at the end of the Marathon give them the option of goal setting for a quit attempt.

5) **Inclusion and Exclusion Criteria**

For all Aims, we will include individuals 18 years and older who are identified as current smokers who are not preparing to quit, and are active in care within the UMMHC system, Northwell Health, VA Central Western MA (VACWM) and Reliant Medical Group (RMG). Active in care is defined as having at least two clinical visits in the past year. If an eligible participant does not already have a smart phone, one will be provided to them, free of charge, for the duration of their participation in the study.

- Exclusion Criteria: Those unwilling to sample nicotine lozenges or participate in the intervention will be excluded. All patients already on NRT will be excluded. All participants who have a FDA contraindication or cautions for nicotine lozenge use (pregnancy, breastfeeding, recent cardiovascular distress, or phenylketonuria) will be excluded. We have chosen to exclude patients with a diagnosis of depression, due to confounding factors.

  Adults unable to consent, individuals who are not yet adults (infants, children, teenagers), and prisoners will be excluded from this study. The Food and Drug Administration (FDA) advises caution for nicotine lozenge use among women who are pregnant. Thus, women who are pregnant at the time of baseline will be excluded from the study. Those who are already participating in another smoking cessation study at the time of screening will also be excluded from the study.

6) **Study-Wide Number of Subjects**

There are three phases of human subjects' involvement in the study. The total number of subjects for all phases is 550 smokers for all recruitment sites.

7) **Study-Wide Recruitment Methods**

There are three phases of human subjects' involvement in the study. In Aim 1, we will refine the integration of the "Take a Break" mHealth tools with 50 smokers; up to 20 smokers will participate in Think Aloud Usability testing and 30 in mini pilots. In Aim 2, we will recruit 500 (approximately 250

from UMMS, 100 from Northwell Health, 75 from VACWM and 125 from RMG) smokers to conduct a randomized trial of the effectiveness of Take a Break. In Aim 3, we will follow participants in the Aim 2 randomized trial for 6 months to evaluate cessation events.

For both Aim 1 and Aim 2, we will recruit UMMHC patients who smoke, have had at least two primary care visits in the preceding 12 month, and are in the Motivation Phase. For Aim 2, we will also recruit from Northwell Health, VACWM and RMG**.** We will not include Aim 1 smokers in Aim 2 recruitment. Please note that as of June 2019, Northwell Health is no longer actively recruiting study participants.

Aim 1-Refining the Take a Break system:
This will be conducted in two steps: 1) Think Aloud Usability sessions,[15,16] and 2) Mini pilots. The Think Aloud usability sessions will be conducted in multiple phases at the UMMS Technology Usability lab, each with 4±1 subjects. These subjects will not be included in the mini pilots. The mini pilots will each include up to 10 smokers who will have access to the system for 3 weeks (training + Take a Break Marathon). The first mini-pilot will split the 3-weeks up into 2 segments. This first segment will consist of all study procedures from the screening through the TTS consultation after Week 1. The second segment will consist of the 2-week marathon and the 3-week follow-up survey. The subsequent mini pilots will test the entire process from start to finish. Throughout and at the end of each mini-pilot, we will conduct qualitative assessments (see mini-pilot assessment question guide). Table 1 indicates the number of participants recruited for each aim. Aim 1 participants will be recruited from a cohort of former research participants. These participants previously indicated they would be interested in participating in future research studies and consented to be contacted. Pilot participants will also be referred to us by our TTS consultant.
Aim 2 and Aim 3- Take a Break intervention and 6 month Follow-Up: Aim 2 and Aim 3 study data collection will involve the recruitment of 500 smokers. Smokers will be recruited from UMMHC, Northwell Health, VACWM, and RMG. Please note that as of June 2019, Northwell Health is no longer actively recruiting study participants.

Recruitment Data Access:

- UMMS recruitment data access: We will use the UMMS EHR to identify smokers. We will seek a HIPAA waiver from the UMass IRB for data access in order to identify potential participants. Once identified, patient data will then be stored in the UMMS regulated environment. At UMMS we will identify patients who smoke and have had at least two primary care visits in the preceding 12 months.
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- VACWM recruitment data access: Research staff at VACWM will handle all VACWM patient data during recruitment. They will seek a HIPAA waiver from their IRB for data access in order to generate list of potential participants.
- RMG recruitment data access: Research Staff at RMG will handle all RMG patient data during recruitment. RMG staff will seek a HIPAA waiver from the UMMS IRB for data access in order to identify potential participants.

Table 1: Pilot Study and RCT Participants				
Research Method	**Participants**	**Duration**	**Number**	**Consent**

Think Aloud Usability (Aim 1)	Smokers from UMMHC Clinics and Inpatient	1 hour	20	Written
Mini Pilot (Aim 1)	Smokers from UMMHC Clinics and Inpatient	3 weeks	30	Written
Take a Break Intervention (Aim 2)	Smokers from UMMHC, Northwell Health, VACWM, RMG	3 week intervention	500	Written
Follow-Up (Aim 3)	Smokers from UMMHC, Northwell Health, VACWM, RMG	6 months	500	Written

UMass Recruitment Strategy:

Opt-out mailing strategy: We will use an "opt-out" recruiting strategy for Aim 2. Smokers will be sent an initial communication that outlines the purpose of the study and informed consent (see *InviteLetter-UMMS-TAB*). A self-addressed, stamped "opt-out" postcard (see *OPTOUT-UMMS-TAB*) will be included with the initial communication; if the patient does not wish to participate, they can mail the "opt-out" postcard in order to be removed from all contact lists for the current study. Potential participants who do not "opt-out" within two weeks will be phoned to determine their interest in the study. As in our prior IRB-approved work, letters describing the study and stating that the patient may receive a phone call regarding the study will be sent to each patient.

Referral Recruitment Strategy*:* We will also recruit study participants that are referred to us by UMMHC clinical partners. To execute the referral we will use an eRefer portal developed by the UMass Center for Clinical and Translational Science Informatics Core. The eRefer portal is a recruitment tool that allows potential research subjects to verbally agree to provide their email and/or cell phone number and be sent only one email and/or text message with information about a research opportunity they are interested in. The message sent to prospective subjects interested in the study only contains IRB approved language (see TAB Invitation Letter) with slight edits tailored to the mode of delivery (email/text instead of mailing). Clinical partners, the 'Referrer' in the eRefer portal (see eReferPortal.Home), enter his/her email address on the eRefer home page, select the 'Take a Break' study from the project list and enter the potential participant's email address and/or cell phone number as preferred by the patient. By providing their email address or cell phone number, the patients verbally agree to be sent the study invitation messages and contacted for recruitment. After the referral has been executed, the eRefer portal provides study staff with the subject's contact information, allowing study staff to contact the subjects. The subjects also receive contact information of the study staff, allowing them to proactively contact the study staff. Data collected in the eRefer portal will be stored in a regulated environment until completion of the project or upon the request of the potential participant. The regulated environment provides applications to a secure network for collecting and storing confidential data. The regulated environment has been securely configured to allow application access via the secure socket layer (HTTPS) protocol. The regulated environment is secured using hardware and software firewalls, along with access restrictions to provide the needed security protocols for the regulatory and Federal standards required. Access is restricted through a Virtual Private Network, a secure RSA token, and only restricted personnel are allowed access to the regulated environment. Our software program will use a secure Application Programmable Interface to send and receive the text messages. These text messages will be sent from toll-free number (18442764493)

Participant Peer-Referral Strategy: After participant completion of the 6 month visit, study staff will ask participants if they would like to give study information (See: Peer-Referral Invitation Letter) to friends and family members who might be interested in participating. If

interested in the study, friends and family can contact the study staff directly with the information provided.

VACWM Recruitment Strategy*:*

Opt-out Recruitment Strategy: Veterans will be sent an initial mailed communication that outlines the purpose of the study and informed consent. If the patient does not wish to participate, they will be instructed to call the VACWM research line and leave a voicemail indicating that they wish to be removed from all contact lists for the current study. Potential participants who do not "opt-out" within two weeks will be phoned to determine their interest in the study. At first telephone contact, study staff will conduct a short telephone screen based on inclusion and exclusion criteria to determine eligibility. Eligible and interested Veterans will then be scheduled for a consent visit, to review the consent documents and, if interested, agree to participate. Once the participant has consented to participate and signed the appropriate documents, an enrollment visit will be scheduled where Veterans will complete study documents and receive NRT.

RMG Recruitment Strategy:

In-person Recruitment Strategy: RMG will implement in-person screening at the time of visit. RMG will utilize the Epic Electronic Health Record (EHR) currently in production at practice sites to identify eligible subjects and obtain participation interest in real-time. Through this process, patients are screened for tobacco use by a Medical Assistant (MA) at the start of their visit. When patients report positive tobacco use, this information is flagged within the EHR and alerts the MA to inquire whether the patient might be interested in participating in the study. The EHR alert is a smart alert that only appears once if the patient is an active smoker age 19 and older who isn't pregnant, has English listed as their primary language, and hasn't been asked to participate in the study before. MA's will be trained on the objectives of the study, the inclusions/exclusion criteria, and the study activities and commitments of participants. The MA enters the response into Epic. Each morning the RMG Research Department will query Epic's Clarity Database to identify patients that expressed an interest in the study. This list of interested patients will then be forwarded to the RMG TAB study staff in order to identify eligible patients. Identified patients will be contacted by telephone within 48 hours of office visit by RMG study staff for screening of study inclusion criteria. During the screening call, the study staff member/recruiter will review the purpose of the study, answer any questions, assess for competency to provide verbal consent and assess study inclusion and exclusion criteria. Patients who screen-in and provide verbal consent will schedule an in-person appointment with RMG study staff to provide informed consent and be enrolled in the study. A total of three phone calls will be made over the course of 3 weeks from the initial contact. On the third call, study staff will leave a short voicemail message asking potential participants to call the RMG Research Department. If patients are not reached during these initial phone calls, an invitation letter (see RMG invitation letter) will also be sent asking potential participants to call the RMG study staff if still interested.

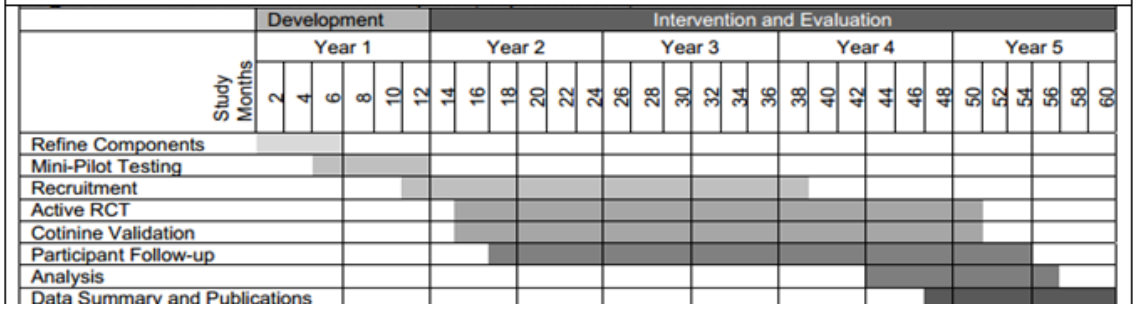
8) **Study Timelines***

Refining the TAB suite of apps will commence in year one of the study. Participant recruitment will begin at the end of year one and will continue until the beginning of year four.

- Aim 1: Recruitment will begin at the end of year one for Aim 1 and will end at the beginning of year 2. Duration of participation in the Think Aloud usability component of Aim 1 will be one hour. Duration of participation in the Mini Pilot portion of Aim 1 will be three weeks.
- Aim 2 and Aim 3: Recruitment will begin at the beginning of year two and will end at the beginning of year 4.

Duration of participation in the RCT through follow-up will be six months. The duration of the study in its entirety is 5 years. Milestones of the study are outlined in Figure 2.

Figure 2: Timeline for Intervention Development, Implementation, and Evaluation



9) **Study Endpoints**

Study endpoints are the conclusion of the three-week marathon and the six-month follow-up. Although unlikely, a safety endpoint is the development of a FDA contraindication to NRT after enrolling in the study. The NRT-sampling component of the study will be discontinued if a FDA contraindication develops. Participation with the TAB app will not be discontinued if a FDA contraindication develops.

10) **Procedures Involved**

Aim 1: Usability Testing: While the smokers are reviewing the content and interacting with the program, we will use "Think Aloud" protocols, where participants will be asked to vocalize thoughts, feelings, and opinions. Think Aloud informs us how the user approaches the interface and what they are thinking about when utilizing the interface. We will develop prompts to guide the user if needed. We will conduct Think Aloud in two phases, which will allow us to capture the majority of usability issues. Each session will last approximately one hour.

We will conduct each usability testing phase with 4±1 users. Think Aloud sessions will be conducted in the UMass Division of Health Informatics mobile usability lab using Morae software. Morae allows for recordings of the subject being tested, including recording clicks, keystrokes, and other events. The results of the Morae Interviews will be transcribed and de-identified. The transcribed interviews will be reviewed by two independent reviewers to inform the finalization of the graphics and interface prior to the mini-pilot. For information about Morae Software, please refer to the attached user guide (Guide for Software Usability Testing with Morae).

Aim 1: Mini Pilot: Each mini pilot will include 10 smokers who will have access to the system for 3 weeks (training + Take a Break Marathon). The first Mini Pilot will test the training and the marathon in 2 different segments while the second Mini Pilot will test the full 3 weeks continuously in one segment. The Mini Pilot will follow the same procedures as outlined in Aims 2 & 3, but without the 6-month follow-up and longitudinal access to the apps. Thus, the participants in the mini pilot will only have 2 in-person sessions per Mini-Pilot segment as opposed to the 3 in-person sessions described in Aim 2+3. Participants in the mini-pilot will be recruited from UMMHC only.

Aim 2 + 3: Components of Take a Break include a brief 3-week experience during which smokers are provided NRT, given the game, encouraged to try a brief period of abstinence, rewarded with recognition points for participation, and allowed continued access to the technology. The game includes Challenge Questions to assess smoking behavior and cravings and provide immediate feedback, and a suite of tools available at the point of need to help develop coping skills.

Randomization: Our statistician will generate a randomization table; the randomization sequence will be conducted in 2 random blocks of different lengths (4, 8) to assure balance between the groups. In Take a Break, the mHealth system will "randomize itself." At the end of the initial assessment our research assistant will access the Take a Break mHealth system on a computer for all participants (both the experiment intervention and comparison groups). When first opened, the research assistant will enter the participant ID and participant mobile phone number from the baseline assessment survey. The Take a Break mHealth system will then look up allocation within the table, and change based on the allocation assignment.

- The Intervention: *Take a Break as an augmentation to NRT-sampling in Motivation Phase*. Take a Break is an intervention in which smokers are encouraged to engage in smoking abstinence. As depicted in Figure 3, the main element, the "Break," is a two-week challenge where smokers report days they are smoke-free. The Break is preceded by a 1-week training challenge where Challenge Quizzes (ecological momentary assessments) collect information to guide the smokers during the Break. At baseline, all smokers will be provided NRT lozenges for sampling. At weeks 1 and 3 of the "Marathon", our Tobacco Treatment Specialist will call all smokers, assess their experiences and collect data.
- The Comparison Group: For the comparison group, implementation will be balanced in all variables except the Take a Break Intervention. We will balance the two groups further by having the comparison (NRT-Sampling group) complete mHealth assessments (without feedback or goal-setting) as an attention control (Table 2).

Table 2: NRT-Sampling Comparison versus Intervention Group

	NRT-Sampling Comparison (Control)	NRT-Sampling PLUS Take a Break (Intervention)
NRT-Sampling	Yes	Yes
Take a Break		
1. Challenges Quizzes and Goal-Setting	**NO***	Yes
2. Smoker2Smoker Messages	**NO**	Yes
3. Coping Mini-Games	**NO**	Yes
4. Recognition and Rewards	**NO**	Yes
Tobacco Treatment Specialist Assessment Calls	Yes, 1 and 3 weeks	Yes, 1 and 3 weeks
*To provide an mHealth attention control, comparison smokers complete mHealth Assessments during 3-weeks, without feedback or Goal-setting		

Participants in the intervention will receive the full tool suite. Participants randomized to the comparison group will only have access to a mHealth assessment tool similar to the "Challenge Quizzes" but without feedback.

Take a Break Mobile Health Intervention Features: The core technology to support Take a Break is a suite of mHealth motivational tools and mini-games.

- *Recognition (Points and Rewards)*: For each of the "mini-games" below, participants have the potential of earning points. In Take a Break, a goal is to have days of smoking abstinence within the two-week period. However, we want to incentivize all participation in self-reported achievement

regardless of abstinence. In addition, all participants will get base points for participating in the Training challenge. Thus, it will not be possible to "lose" the Break. Based on their level of participation all study participants will receive CVS gift cards totaling either $5, $10 or $15.Study participants at RMG will receive checks (mail after each visit) in the same amount as the CVS gift cards. The lowest 25% of participants will receive $5, the middle 50% will receive $10 and the top 25% will receive $15 gift cards.

- *Take A Break Peer Community*: Intervention smokers will be able to support each other in a private online community. Peer-to-peer communication can enable information exchange, provision of social support (e.g. emotional and instrumental) and establishment of group norms.[17] Online communities also improve engagement with other intervention functions. Those currently in a Marathon will be allowed to share their progress (and points) with other smokers in the 2-week Marathon. Those who have completed the Marathon will be able to see the status of others progressing. We will also regularly post topics designed to encourage participation in the community. Our group has prior experience developing online communities. In our prior RCT (1R01CA129091-01), smokers participating in a web-assisted tobacco intervention were provided an opportunity to participate in an online community. Community participants were more likely to take advantage of other intervention functions. Community participants were also more likely to quit smoking (24 to 28%).
- *Coping mini-games*: We have multiple options for coping mini-games to include in Take a Break.
  - *Distraction Apps:* To distract smokers from cravings and prevent relapse, we developed and evaluated the smartphone game "Crave Out!" a multi-level pattern memory challenge (Figure 4).[18,19] We conducted a pilot study recruiting smokers from outpatient and inpatient settings (n=30), and we demonstrated that Crave Out could potentially reduce cravings. In addition to Crave-Out, we have identified 3 free apps that can also be used for distraction from smoking cravings. They are:

Figure 4: Crave Out! A Coping Mini-Game

  - *WordScapes:* This game combines the best of word searching and crosswords for tremendous brain challenging fun. Within each crossword puzzle, the participant will drag their finger to create a word that they see using the circular series of letters. The number of letters in the circle depends on their respective level (the higher the level , the more letters)**.** Depending on the number of the words , the participant will be rewarded with various points based off of the completed level.
  - *Piano Tiles*: The objective of this game is to press all of the black tiles on the screen without hitting any white tiles. The participant will try to do it as quickly as possible until they make it to the finish line.
  - *Flow Free*: The participant will use their finger to drag to connect matching colors with a pipe to create a flow. The goal is to pair all of the colors and cover the entire board with pipe to solve each puzzle.
  - *Relaxation Apps*: Relaxation is recommended as a behavioral tool in the current Treating Tobacco Use and Dependence guidelines.[20] In preparation for this application, we conducted a heuristic

review of popular relaxation or meditation Apps currently available on iTunes. We found ten Apps relevant to our review. The most popular used a combination of guided deep breathing and sounds to induce relaxation. Relaxation through deep breathing has been used in smoking cessation,[21] and we will use these popular and evidence-supported principles. We have identified 3 free apps that can be used to help relax during a smoking craving. They are:

- *Take a Break*: This app is designed to walk the participant through a guided breathing exercise to help with relaxation.
- *Calm*: This app can help the participant relax their whole body through a series of auditory guided breathing and relaxation exercises.
- *Breathe2Relax*: For this app, the participant can watch and participate in a series of demonstrations to help them relax. These include: diaphragmatic breathing, learning about stress, and engaging in reading, writing, and practicing different types of relaxation.

- *"Smoker 2 Smoker" Motivational Messages*: Our team has developed and evaluated a computer-tailored motivational messaging system. Messages were evaluated within the context of a web-assisted tobacco intervention (R21-CA089011, 1R01CA129091-01).[22-26] Expert-written messages were developed through a group review, and were guided by current guidelines[2] and Social Cognitive Theory.[27] Smoker-written messages were written by current smokers responding to scenarios that varied on readiness to quit smoking. We have demonstrated that the messages increased engagement in the online smoking intervention and increased six-month smoking cessation outcomes. As with the other mini-games, smokers will receive points for viewing the messages. Smokers can also receive bonus points by writing their own messages.
- *Challenge Quizzes*: These brief games will consist of 1 to 3 questions with multiple-choice answers. The purpose of the Quizzes is two-fold: 1) to impart tailored feedback (brief educational messages designed to change perceptions about smoking cessation); and 2) to assess situational characteristics, abstinence behaviors, and cravings. Smokers will have up to 3 Quizzes per day. Players will receive increasing points for the number of consecutive reports, regardless of abstinence or lack of abstinence.

<u>Take a Break 3-week Marathon & Longitudinal Access</u>:

- *Week 1 TRAINING Challenge*: The purpose of the Training Challenge is to collect information about smokers' daily life experiences. Smokers may think about challenges they may encounter when they "Break" with smoking. Players will earn points by completing Challenge Quizzes. In addition to providing data, the use of the Challenge Quizzes will provide smokers experience with interacting with the game so they will be better prepared to "Take a Break." At the

Figure 3: Take a Break Components

completion of the Training Challenge, players will be asked to set a goal for number of days abstinent during the Break challenge.

- *Week 2-3 The BREAK NRT-sampling experience and mHealth tools*: The Break is a two-week experience. During the Break, smokers are encouraged to initiate abstinence from smoking and maintain abstinence for as long as possible. Consistent with a motivational intervention, smokers will not be forced to initiate abstinence on the first day of their assigned Break period, but will earn points for each day they reply to the ecological momentary assessment through our two-way texting system. During the Break, smokers will be supported by our evidence-based and effectiveness-tested mobile health tools in the Game. At the end of the Break, players will meet once more with our study staff. All Intervention participants will receive gold, silver, or bronze level awards for participation and will be asked if they would like to set a quit date. Current smoking will be determined through self-report and verification with a carbon monoxide breath monitor. Smoking cessation verification will be performed at the study site they were recruited at during the participant's last in-person session.

Take a Break Game Longitudinal Access: After the immediate skills-building experience, smokers in the intervention group will have access to the game during the 6-month follow-up period. This access includes motivational text messages sent from a toll-free number **(**18442764493) , distraction and relaxation apps, and access to the study TTS. Thus, once they are ready for a future quit attempt, these intervention tools will be available to them. Smokers who have already completed a Take a Break experience may then choose to join new challenges, trying additional abstinence periods. Thus, the initial 3-week experience period serves as an intervention itself, and as a practice use of the game so that the smoker will be better prepared for the next quit attempt. NRT will not be provided by investigators after the first 3-week experience. Upon completion of study participation after the 6-month follow-up visit, participants (both Intervention and Control) will be asked if they are interested in participating in future research activities. Interested participants will be asked to sign an authorization to contact form (See TAB.authorization_to_contact.7.19.17).To increase engagement with intervention tools after the 3-week follow-up, we will send an additional texting assessment to intervention participants. These smokers will be asked to rate their current mood using the question, "How would you rate your mood right now?" Participants will be prompted to reply based on the response options "1= good, 2=ok, or 3= bad". We will ask this question for a period of 5 weeks, twice a week for a total of 10 assessments. Following this assessment, study participants will be randomly asked whether they would like to speak to the TTS or reminded to utilize the distraction or relaxation mobile apps previously downloaded.

- For study participants unable to come in person to complete the 6- month follow-up visit, we will mail a letter [see "Request to complete_TAB_6mo_fuvisit"] asking them to complete the 6 month follow up survey and mail back in the included pre-postage envelope.

NRT-Sampling (provided to both intervention and comparison groups):

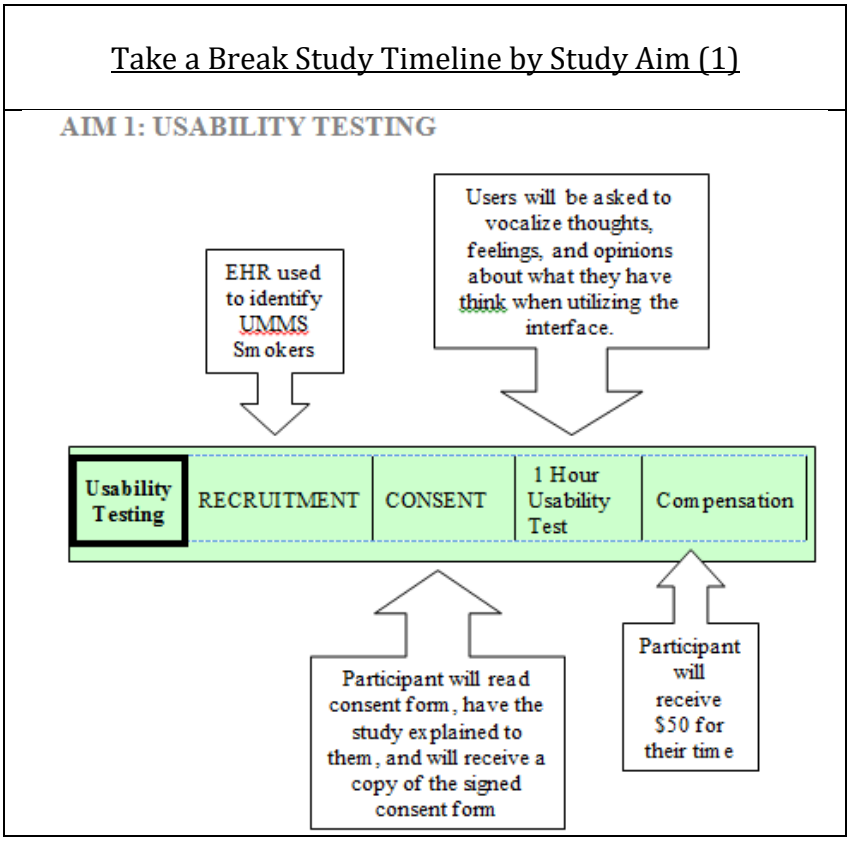
During the initial recruitment session, we will provide smokers' 1 box (81 Nicorette4-mg mint) of nicotine lozenges purchased over the counter from a commercial vendor. Participants can choose to use or not to use the NRT. It will be provided to participants, but use of it is optional. (See Section #32 for details on dispensing procedures.)

Quality Improvement Interviews: The researchers would like to interview UMass Memorial nurses and hospital leadership to better understand the current initiatives related to tobacco cessation in the hospital setting and how a quality improvement mobile health tool for tobacco cessation could enhance care for current tobacco users staying at the hospital. The purpose of interviewing hospital leadership is to gather insight into current tobacco cessation initiatives and their insight into whether this tobacco cessation tool could improve the quality of care given to tobacco users admitted to the hospital. We will interview 10

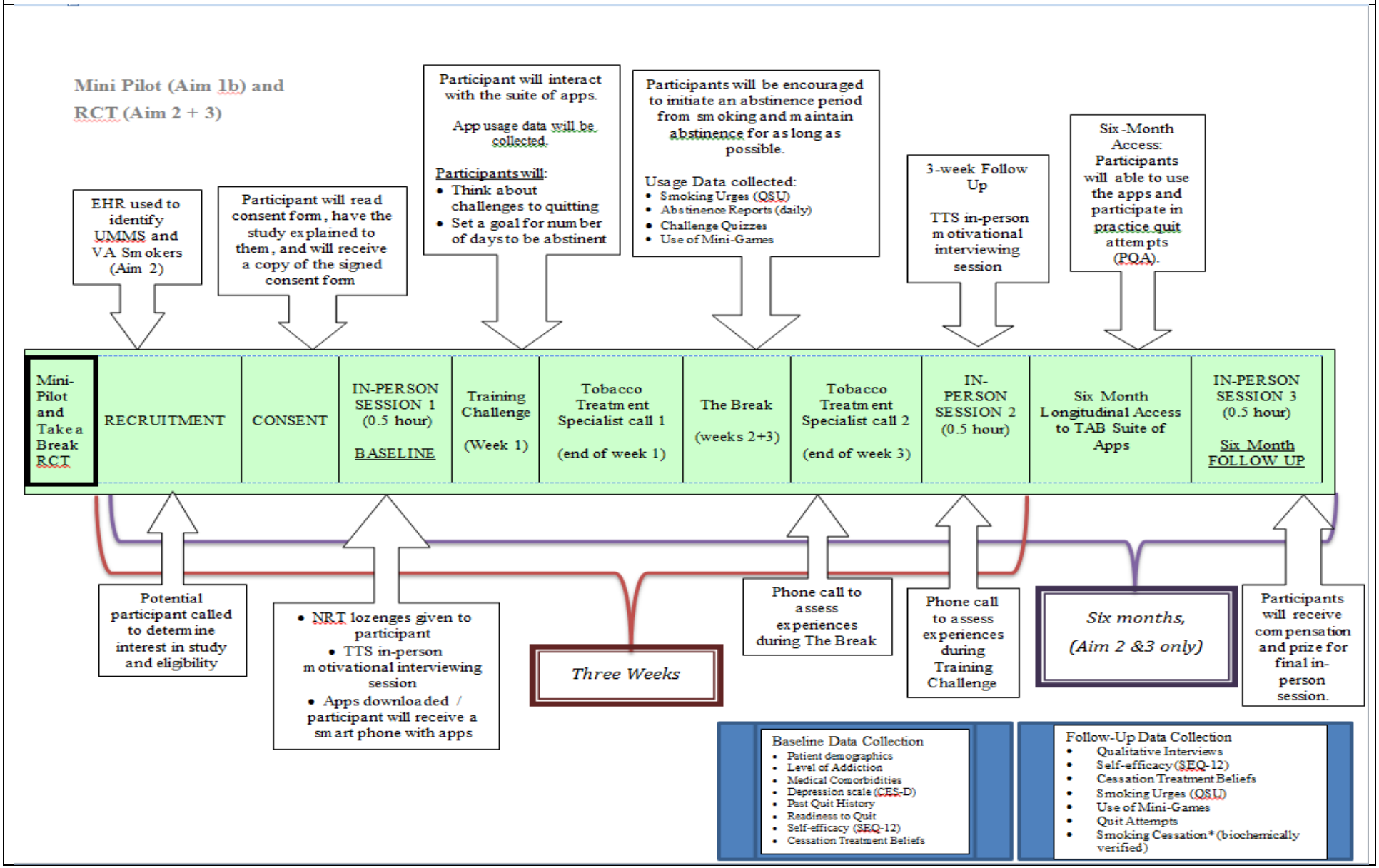
people in hospital leadership at UMass Memorial. The purpose of interviewing nurses would be to understand more fully the work they currently perform on their hospital floor, how they identify tobacco users on admission, the actions taken to assist tobacco users during their hospital stay and their insight as to whether this tobacco cessation tool would benefit tobacco users in the hospital. We will interview 20 nurses at UMass Memorial.

Participants will be interviewed for approximately 45 minutes and will be audio-recorded. The interviewer will remind participants that the interview is being audio-recorded and as a measure to protect your confidentiality, they will be asked not to mention their full name once the interview recording starts. Participants will give verbal consent and will be given a Fact Sheet for their records. They will be reminded that the data will be protected and should data be lost or stolen, it poses minimal risk to participants. The recorder will be stored in a locked drawer, the data will be protected in the password-protected PI's UMass Medical QHS department folder, and the data will be destroyed at the end of the study. The participants will be compensated for their time with a $50 Amazon gift card. Funds from a training grant funded by NCI for post-doctoral fellows in Cancer Research are being utilized for the incentives of the Quality Improvement Interviews. As part of the training grant's budget, each fellow is awarded funding to conduct their own research. The research & human subjects portion of the grant are not provided in section 7.0 because the grant does not provide the specifics of the research activities.

Below are timelines of the events for each study aim. Described in the timeline are the events that will occur at each of these study points.



Take a Break Study Timeline by Study Aim (2 &3)



11) **Data and Specimen Banking**

Data collection for this project includes web-based, telephone, and in-person methods for Aims 1, 2, and 3. (Table 3). All primary study data collected will be centralized and stored within the UMMS Regulated Environment. Paper copies of consent forms and data collection tools (baseline and follow-up surveys) will remain at the study-specific sites in a locked cabinet. Only CITI trained study staff will be able to access to primary study data. Data files cannot be transferred electronically outside of the regulated environment.

Aim 1: *Usability think-aloud interviews*. We will conduct usability interviews using the Morae software and laptops with full data encryption. The Morae recording will be transferred to a server in the UMMS IS regulated environment and removed from the laptops.

Aim 1 + 2: *Mini Pilot + RCT.* Surveys conducted on the telephone and in-person (see Table 3 for specific surveys) will be recorded within REDCap at the time of completion. TAB activity will be collected by UMMS web-based servers and stored within the UMMS IS regulated environment.

Table 3: Data Collected and Source

Variable	Source				Stage of Collection			
	EHR Registry	**Baseline**	**App Metrics**	**Follow Up**	**Screening**	**Baseline**	**Intervention**	**Follow Up**
Demographics (age, gender, race)	Y	Y	N	N	Y	Y	N	N
Level of Addiction (FTND)	N	Y	N	N	N	Y	N	N
Past Quit History	Y	Y	N	N	N	Y	N	N
Readiness to Quit	N	Y	N	Y	Y	Y	N	N
SES/Housing Stability	N	Y	N	N	N	Y	N	N
Depression (CES-D)	N	N	N	N	Y	N	N	N
Alternative Tobacco Use & e-cig	N	Y	N	Y	N	Y	N	Y
NRT Use	Y	Y	N	Y	Y	Y	N	Y
Alcohol/Illicit Drug Use	N	Y	N	Y	N	Y	N	Y
Smoking in Household	N	Y	N	N	N	Y	N	N
Cessation Treatment Beliefs	N	Y	N	Y	N	Y	N	Y
Health Behaviors (exercise, sleep diet)	N	Y	N	Y	N	Y	N	Y
Health Literacy	N	Y	N	N	N	Y	N	N
Medical Comorbidities (SCQ)	Y	Y	N	N	Y	Y	N	N
Perceived Stress	N	Y	N	Y	N	Y	Y	Y
Provider Behavior	N	Y	N	N	N	Y	N	N
Religion	N	Y	N	N	N	Y	N	N
Self-efficacy (SEQ-12)	N	Y	N	Y	N	Y	N	Y
Smoking Urges (QSU)	N	N	Y	Y	N	N	Y	Y
Social Support/Family (mMOS-SS)	N	Y	N	N	N	Y	N	N
Technology Literacy	N	Y	N	N	N	Y	N	N
Triggers	N	Y	N	N	N	Y	N	N
Challenge Quiz Completion	N	N	Y	N	N	N	Y	N
Days Abstinent	N	N	Y	N	N	N	Y	N
Smoking Cessation* (biochemically verified a 3wk, 6 months)	N	N	N	Y	N	N	N	Y
Time to First Quit Attempt	N	N	N	Y	N	N	N	Y
Use of Apps/Mini-Games	N	N	Y	Y	N	N	Y	Y

Aim 3: *Follow-Up.* Surveys conducted during follow-up will be stored in the same manner as in Aim 1 and 2. Biochemically verified smoking cessation results will be stored in REDCap. Biochemically verified smoking cessation tests will only be conducted with participants that used the optional NRT.

Quality Improvement Interviews: Participant interviews will be audio-recorded. The interviewer will remind participants that the interview is being audio-recorded and as a measure to protect their confidentiality, they will be told not to mention their full name once the interview recording starts. They will be reminded that the data will be protected. In the unlikely event that the data is lost or

stolen, there is minimal risk to participants. The recorder will be stored in a locked drawer in a locked office. Upon transcription of the interviews, the data will be stored within the UMMS Regulated Environment and saved within a password-protected folder created for this aim of the study. The list of participants will be stored separately from the transcribed interviews.

Data will not be released to other researchers. Data will be stored for 6 years.

12) **Data Management**

Data Analysis Plan: In Take a Break, we are interested in both the immediate and long-term effects. Measuring immediate and long-term effects allows us to demonstrate the pathways (brief abstinence, and enhanced self-efficacy) by which long-term quit attempts and cessation result.[4] Compared with the NRT-only comparison, the Take a Break intervention group will have:

- Hypothesis 1: (Aim 2) *Greater mean number of days abstinent during the immediate Marathon Days Abstinent:* We will measure the difference in the number of days abstinent reported by mHealth assessment. The abstinence interval is 2 weeks, and an abstinence assessment will occur daily. Thus, days abstinent can vary from N to 14 days.
- Hypothesis 2: (Aim 2) *Greater increase in self-efficacy at the end of the 3-week experience:* Change in Self-Efficacy is defined as the difference in reported self-efficacy (SEQ-12)[28] comparing baseline and follow-up at the end of the 3 week experience for intervention and NRT-only comparison patients.
- Hypothesis 3: (Aim 3) *Lower time to first quit attempt (1-survival in longitudinal analysis) Time to first quit attempt (mean survival) – Primary Outcome*: Quit attempts and cessation will be assessed at follow-up surveys at 3 wks and 6 months. Quit attempts will be assessed using the Timeline follow back method, which uses a calendar to reconstruct smoking behaviors.[29]
- Hypothesis 4: (Aim 3) *Higher rate of point prevalent cessation measured at 6 months Six-month point prevalent smoking cessation*: Smoking cessation trialists have recommended assessment of smoking cessation in randomized trials of motivational interventions of point prevalence cessation.[30,31] The Take a Break trial is defined as a test of treatment to motivation cessation (also termed cessation induction). As Hughes and colleagues for the Society for Research in Nicotine and Tobacco Workgroup on Measurement note, point prevalence cessation is often the best measure for motivation phase trials.[31]

Statistical Analyses: To preserve the power of randomization, all primary analyses will be on an intent-to-treat basis. However, secondary analyses will explore dose-response effects among those with variable levels of adherence to the intervention, as ascertained by survey. All analyses will be two-sided and alpha error will be set at 0.05. We will begin the statistical analysis by examining univariate statistics (means, medians, standard deviations and 95% confidence intervals) and distributions. We will examine the balance of participant characteristics by study groups and account for any imbalances in our multivariable analysis. As appropriate, group differences will be tested using chi-square tests of independence (categorical variables), Z-test or t-test (continuous variables) or the equivalent non-parametric tests depending on the distribution of the variables. In accordance with best practice, differences in baseline characteristics of the intervention and comparison groups will be established based on standardized differences, rather than on tests of statistical significance.[32,33]

- Hypothesis 1: The mean number of days abstinent will be greater in the intervention than in the control. Both groups will be observed for (t=) 14 days. If we assume X1 to be the number of days abstinent in the intervention group and X2 to be the number of days abstinent in the control group, then X1~Poisson(tλ1) and X2~Poisson(tλ2) where λ1 and λ2 are mean days of abstinence in the two groups. Our null hypothesis is that these two rates are similar. In order to test this hypothesis, we will first compute the number of days abstinent for each individual over the 14 days of the "Break" portion of the Marathon and obtain the mean number of days abstinent within each group. We will use the Z-test to test whether difference in the mean days of abstinence between the groups is statistically significant. If we find significant differences in the distribution of the characteristics of subjects in the two groups, then we will include them as covariates in a multivariable Poisson regression model with the number of days abstinent as our main outcome and group as the main independent variable.
- Hypothesis 2: The self-efficacy (SEQ-12) scores will be higher in Take a Break group than in the control. The SEQ-12 is a 12-item questionnaire with 6 questions under each domain. Two composite scores are computed for each of these domains by adding the individual items. These data will be collected at baseline and at the follow-up. The aim is to assess the effect of intervention over the immediate period, i.e., do the scores improve from baseline to the end of the Marathon more for the intervention group than the control group. We will compute the scores at baseline and 3 weeks for each patient in the two groups. We will evaluate whether the intervention differences change over time (i.e., is there a intervention and time interaction?). To address this question, we will use a random-effects model of the form: yijt = α + γi + βj + δt + (βδ)it + uij + eijt where, yijt is response at time t for the j-th subject in the i-th group, α is the intercept, γj is the vector of effects associated with covariates, βi is the main effect for the intervention group, δt is the main effect for time, (βδ)it is the effect for the interaction between intervention group and time, uij is the random effect corresponding to the j-th subject in the i-th group (assumed to be N(N,+ ₂ ₫)), and eijt is the term accounting for sampling variability (assumed to be N(N,+□ ₫)). The coefficient (βδ)it is the estimate of the interaction term which, if significant, indicates that the intervention effect varies significantly with time. We will first generate the variance-covariance matrix to determine the appropriate covariance structure. We again perform model diagnostics to assess fit.
- Hypothesis 3 (Primary Hypothesis): Time to first quit attempt will be less in the intervention group than in the control group over the period of the study. Our outcome of interest here is the survival time (in our case time to quit), and we want to compare the survival time in the two groups or assess the relationship of group status to survival time. We will obtain the survival curves for the two groups and plot the Kaplan-Meier curves. We will use the log-rank test to test the hypothesis of no difference between the two groups. This test assumes independence in the observations and independence between the censoring and survival distributions. We will also construct Cox-proportional Hazards regression models to assess the association between group and attempt to quit smoking. This is a semi-parametric model which does not assume any distribution for the baseline hazard and is defined as: h(t;x1,x2,. . .,xk) = λN(t)exp(λ1x1 + λ2x2 + … + λkxk) where, λo(t) is the baseline hazard at time t and x1,x2, . . . , xk are k independent covariates. No assumptions are made regarding the baseline hazard function. Let X1 denote group status (1=intervention; N=control). Then exp(λ1) is the hazard ratio for the subjects in the intervention group versus those in the control group and indicates the ratio

of instantaneous probability of an event in the two groups. A positive hazard ratio implies that the intervention group will have a shorter time to quit than the control group. We will express the risk estimates as hazards ratios, 95% confidence intervals, and p-values. As with the previous aims we will also assess model fit.

- Hypothesis 4: Point prevalent cessation measured at 6 months will be greater in the Take a Break intervention than in the control group. The main dependent variable is patient tobacco cessation rate. The primary independent variable is assignment to intervention or control group. We have designed a patient-level analysis around point prevalence cessation based on the following question "Do you currently smoke cigarettes (smoked even 1 puff in the last 7 days)?" We will use a two-sided chi-square test for equality of proportions to test whether the quit rates differ between the groups. If we need to adjust for any covariates, we will include them in a multivariable logistic regression model with smoking cessation as the outcome and group status as the main independent variable. Using mediation analysis, we will examine the potential mechanisms through which we anticipate the intervention may produce a beneficial effect.[34]

Power Analysis: We will make every effort to maximize participant retention in the study. For our short-term evaluation, we do not expect high rates of attrition; however, we approximate that there will be about 15-20% attrition based on previous studies. Thus, although we plan to randomize 500, our power calculations for outcomes are based on 400 completing follow-up. We will monitor recruitment and retention, and inflate our sample as needed to achieve the resulting sample of 400 completing 6-months. We will estimate potential bias due to dropouts in our study and perform a series of sensitivity analyses to understand the extent of this bias. We will assess the extent of missing data by treatment group for each time point. Power calculations are based primarily on the two primary hypotheses (H1 and H3) and were conducted in the statistical software PASS.[35] Again, power calculations are based on 400 subjects with complete data (even though we plan to randomize 500).

- Hypothesis 1: We are interested in testing whether the mean number of days in the intervention group is higher than that in the control group after 14 days. Assuming 2NN subjects in each group observed over 14 days, we have 8N% power to detect a difference in mean number of days abstinent (Hypothesis 1) as small as 0.08. In the prior practice quit attempt study, 80% of participants reported one quit attempt during a six-week interval, thus we have assumed a base rate of 1 day abstinent in the comparison group. This is based on a one-sided test to test the ratio of two Poisson means and assumes a significance level of 0.025.
- Hypothesis 2: We assumed the mean SEQ-12 to be 38.6 in the control group as reported by Wangberg et al and a standard deviation of 3 (inferred from their paper but not reported by them). A sample of size 200 in each group will achieve 80% power to detect a difference of 0.8 between the group means. This was based on a two-sided two-sample t-test and a significance level of 0.05.
- Hypothesis 3: We have used power calculations for survival analyses. Our outcome of interest is time to event (first quit attempt). A sample of size 200 in each group will have 80% power to detect a hazard ratio of 1.88 when the proportion quitting in the control group is 0.30 and that in the intervention group is 0.49. This calculation was based on the log-rank test and assumes that we only conduct one sequential test using the O'Brien-Fleming spending function to determine the test boundaries, that the survival times are exponential and a two-sided significance of 0.05. If we conducted 3 sequential tests, the detectable hazard ratio is 1.89.

- Hypothesis 4: We assumed a control cessation rate of 15%, 48 a two-sided significance level of 0.05. A sample size of 200 in each group will achieve 80% power to detect a difference of 11% (quit rate in the intervention=26%) in quit rates between the two groups. This is based on a Z-test with pooled variance.

Data Security: We will handle data differently for UMMS, Northwell Health, VACWM and RMG smokers, per each institution's protocol. UMMS and RMG are covered under the same UMMS IRB docket while Northwell Health and VACWM have protocols independently reviewed by their own IRB. Table 4 summarizes data collection. There will be no transfer of patient data between study sites and UMMS prior to recruitment into study. Screening data collected for recruitment will be password protected and stored behind each study site's firewall. Patient contact information provided through the eRefer portal will be encrypted at rest and during transit using Secure Sockets Layer (SSL) standard security protocol. Each study site will have access to only its own identifiable patient data with the exception of UMMS study staff which will have access to all participant identifiable data. Once smokers are enrolled in the study, their intervention data will be stored on UMass servers. This will be done by entering the data directly into the UMMS REDCap database by study staff at each study site. This data will be stored in the regulated database servers and accessible through a secure form and a password-protected connection.

Table 4: Data Collection Source and Storage

Source	Collected From	Personal Identifiers	Collected By	Data Storage
Aim 1				
Think Aloud Usability	Smokers participating in the usability sessions at UMMS Technology usability lab	Yes (identifiers are collected and stored in encrypted form)	UMMS database server in the regulated environment	UMMS IS regulated environment
Mini pilot	Mini Pilot will match Aim 2 data collection plus an additional qualitative interview	Yes (identifiers are collected and stored in encrypted form)	See Aim 2 procedures. Qualitative interviews are directly entered into the regulated environment through a secure REDCap form	UMMS IS regulated environment
Aim 2 Recruitment				
Recruitment – UMMS	Smoker data will be collected from UMMS EHR and the eRefer portal	Yes (identifiers are collected and stored in encrypted form)	All data extracted from EHR will be stored in the regulated environment. Data collected from eRefer portal will be encrypted.	UMMS IS regulated environment
Recruitment – Northwell	Smoker data will be collected from Northwell EHR	Yes (identifiers are collected and stored in encrypted form)	All data extracted from EHR will be stored in the regulated environment	Northwell IS regulated environment
Recruitment – VACWM	Smoker data will be collected from VA EHR	Yes (identifiers are collected and stored in encrypted form)	All data extracted from EHR will be stored in the regulated environment	VACWM IS regulated environment
Recruitment – RMG	Smoker data will be collected from RMG EHR	Yes (identifiers are collected and stored in encrypted form)	All data extracted from EHR will be stored in the regulated environment	RMG IS regulated environment
Aims 2 and 3 Intervention				
Baseline and 1-week	In-person (baseline) and the phone	Yes (identifiers are collected and stored in encrypted form)	Will be directly entered into the UMMS database server in the regulated environment	UMMS IS regulated environment

1-week TTS Call	Telephone	Yes (identifiers are collected and stored in encrypted form)	Will be directly entered into the UMMS database server in the regulated environment	UMMS IS regulated environment
System use (3 weeks intervention)	Smokers responses to text messages from system	Yes (identifiers are collected and stored in encrypted form)	UMMS database server in the regulated environment	UMMS IS regulated environment
Follow-Up at 3 week and 6 months	In-person and Telephone	Yes (identifiers are collected and stored in encrypted form)	Will be directly entered into the UMMS database server in the regulated environment via REDCap	UMMS IS regulated environment

Data Security at Northwell Health: The Department of Research Information Systems at Northwell Health provides resources and support needed in a research environment, and includes IT Security for the research enterprise at Northwell Health. The IT Security team provides many services to help the Northwell Health research community protect electronic protected health information, or ePHI, including vetting nonstandard systems (hardware & computing resources) and nonstandard applications and software to ensure security and compliance, granting temporary access to an electronic medical record for research monitors and auditors. EMR access is controlled with unique user IDs, password protection, levels of access based on research needs, termination of access, and automatic logoff after inactivity. Workstations are secured and protected from public view, and data is maintained and backed up on a secure health-system server. IT Security also provides tools for secure data storage and archiving, such as dedicated PHI drives, and encryption of portable devices like external hard drives and USB drives. All paper forms that contain identifying information will be kept double locked (ie. lockable cabinet, in a locked room) to maintain their security. These paper forms will remain at the study site throughout the duration of the study. All study data forms will only contain participants' unique study identification number, using reference system maintained by the PI and study research staff. All electronic study data will be kept in password protected files on secured network servers. Only IRB approved study personnel will have access to the data.

Usage data will be temporarily stored on the mHealth system until it can be transferred to the UMMS IS regulated database servers upon network access. To prevent access to this data, all security precautions will be taken. This data will be encrypted using industry standard encryption algorithms. We will support remote-wipe capabilities in case a phone is stolen.

Data Security at VACWM: Each participant will be assigned a subject number upon entry into the study by the secure mHealth system at UMMS, and all measures/records will be tracked using only this number. The subject number will not be based on any information that could be used to identify the Veteran. A master list matching personal information with research codes will be kept separate from all personal information in a separate folder on a secure VA network drive and a secure UMMS server. Data collected through telephone and in-person questionnaire and study instrument data collection will be collected via hard copy and will be promptly entered into REDCap, which is hosted in a regulated environment stored in regulated, secure UMMS database servers. At screening, personal identifiers (name, address, phone number, and e-mail address) will also be promptly entered into REDCap, separate from survey data, and maintained on secure VA servers. All data collected in the project will also be stored in a regulated

environment in the data center maintained by the UMMS Information Services department. The UMMS regulated environment provides applications on a secure network for confidential data. The regulated environment has been securely configured to allow application access via the secure socket layer (HTTPS) protocol. The setup of regulated environment provides the needed security protocols for the regulatory and Federal standards required. Access is restricted through a Virtual Private Network and a secure RSA token and only restricted personnel are allowed access to the regulated environment. The Regulated environment is secured using hardware and software firewalls, along with access restrictions to enforce governmental policies requiring to enforcement.

Paper copies of all documents will be stored in a locked office within a locked cabinet in Worcester Plantation Street, Biotech 4, Room 3432. Personal identifiers (name, phone number, address, & e-mail) will be obtained at study screening to contact Veterans. This information will be entered directly into a Microsoft Excel file on a secure server behind the VA firewall as well as into REDCap at the time of screening, and kept separate throughout the study from the participants' other information (e.g., their self-report measures/clinical interviews) which will only be identified by their participant number. The hard copy data will be kept in locked drawers in Worcester Plantation Street, Biotech 4, Room 3432, which will be in a locked, secure office within the VA. Any electronic data not entered into REDCap (study regulatory documents, and tracking spreadsheets) will also be kept on a secure VA Research drive network.

13) **Provisions to Monitor the Data to Ensure the Safety of Subjects**

All data will be stored in a HIPAA compliant regulated environment and access will be only through a secure VPN network. All smokers' related identifiers are encrypted in the database. The biostatistician of the Quantitative Methods Core will organize data security and archiving.

In no way will individual participant data be released to the public or cited in a publication. We have substantial experience with successfully implementing these methods.

To ensure the safety of subject, the telephone screening script refers patients who screen ineligible due to possible depression to contact their primary care provider if they need to talk about how they are feeling.

Data and Safety Monitory Board: This trial is not a Phase III study of a pharmaceutical treatment, but as we will be including NRT and our behavioral intervention, we will establish a Data and Safety Monitory Board (DSMB). The DSMB will review protocols and consent documents for this trial, monitor safety issues throughout the study and the quality of the accumulating data, provide guidance on interim analyses and stopping rules. They will also serve as a liaison among the study investigators, the University of Massachusetts Medical School's Office of Human Research Protections (IRB), and the National Institute of Health (NIH). The DSMB will be comprised of persons with no direct involvement in the study or conflict of interest with the research team conducting the randomized trial. The DSMB will include individuals with expertise in: 1. Clinical research in Tobacco; 2. Health Informatics and/or Information Technology intervention research; and 3. Biostatistical experience. Once patient recruitment for the trial has begun, the DSMB will meet two times per year or more frequently as determined by the DSMB members. The Board and the PI will decide upon the format of the meetings. The PI may present

information about the study to the Board, but the PI will not be present for the DSMB's discussion or voting. Additional telephone conferences will be held if doing so is recommended by the DSMB.

14) **Withdrawal of Subjects**

We do not anticipate withdrawing any participants without them being informed. If study staff are notified of a contraindication to NRT use, the participant will be notified and advised to discontinue NRT use. If this event occurs, the event will be documented by the study staff member and will report it to the PI the same day. Participants who develop a contraindication to NRT after being enrolled in the study, will not be removed from the study, as use of NRT is not mandatory, but is available, to the study protocol. Participants can opt out of the evaluation at any time, and data collection will stop for those participants.

15) **Risks to Subjects**

The risks of the study are not high. Risks to participants relate mostly to misinterpretation of what is research and what is loss of confidentiality. The major risk is the accidental disclosure of information; however as noted, every precaution will be taken to prevent this and the study team has an excellent track record of protection of confidential data. The data will be stored in a HIPAA-compliant regulated environment and access will be only through a secure VPN network. All smokers' related identifiers are encrypted in the database.

Participants will be provided with NRT at the same dose available over-the-counter, to be used if the participant desires. Nicotine lozenges will be used because they are available over-the-counter, they can be used as needed, and many smokers find them more palatable. As this treatment has less nicotine than cigarettes, it is in general a risk reduction from active smoking. Please refer to the Product Information (see Attachment-Nicorette Lozenges Product Information) for potential risks of Nicorette Lozenges. As we review our list of smokers for proactive recruitment with their physicians, we will exclude any patients who their provider deems is a risk for NRT. All participants who have a Food and Drug Administration contraindication to nicotine lozenge at baseline will be excluded. We will monitor participants for development of contraindications during the study period. If one develops, we will advise the participant to discontinue NRT use and to discuss it with their doctor. Participants who develop a contraindication will not necessarily be removed from the study in its entirety, just the NRT-sampling aspect.

Participants may feel embarrassed, uncomfortable, or discouraged as a result of the study (for example, if they have difficulty maintaining short-term abstinence, if they have difficulty understanding how to use the app, etc.). All feelings will be addressed with sensitivity, compassion, and empathy by the study staff. As with all other aspects of the study, any feelings or emotions discussed with study staff will be kept confidential.

16) **Potential Benefits to Subjects**

The major benefit to smokers is the additional resources to encourage smoking cessation and the potential for supporting cessation attempts and maintenance and the resulting health benefits.

17) **Vulnerable Populations**

This study does not involve individuals who are vulnerable to coercion or undue influence, such as cognitively impaired adults, persons who have not attained the legal age for consent to treatments or procedures, pregnant women or neonates of uncertain viability or non-viable neonates.

UMMS employees will be recruited for the Quality Improvement Interviews. The researchers will work with the nursing supervisors to see if staff nurse interview times and locations, generally, could be incorporated into the normal workflow. This will ensure there is a private space for an interview and that the study will not interfere with normal operations. If the supervisor believes interviewing during working hours is feasible with adequate coverage, then this will be an option for staff. Otherwise, all interviews will be performed outside of working hours and supervisors will not be aware of which staff member does or does not participate.

The supervisor will introduce the study to their staff and interested staff will then contact the researchers. If the interview is performed outside of regularly scheduled work hours, this information will not be shared, but the participant may share their participation if they wish. If staff elect for an interview during working hours, permission of their supervisor may need to be sought. This will be communicated to the staff member by the researchers during recruitment.

The following safeguards have been established to protect the rights and welfare of this population:

- Researchers will not inform supervisors of nurses' participation status.
- Under no circumstances will participation records be available to supervisors.
- Individuals involved in research processes (recruitment, consent, & interviewing) will not be involved in the employee evaluations and assessments.
- Participation in this study will have not have any effect on grades, employment records and/or performance reviews.

18) **Multi-Site Research**

This is a multi-site research study. Recruitment will take place at UMMHC, Northwell Health, VACWM and RMG. Please note that as of June 2019, Northwell Health is no longer actively recruiting study participants. To ensure consistency among all research sites, all recruitment documents will be created by UMMS staff. All sites will have the most current version of the protocol, consent documents, and HIPAA authorization. All required approvals will be obtained at each site. If necessary, all modifications will be communicated to staff at each site and approved before the modification is implemented. Each site will safeguard data as required by local information security policies. All study staff at each recruitment location will conduct the study according to protocol. Any SAEs will be reported within one day of occurrence to the UMMS PI and project coordinator. All non-compliance or deviations from the study protocol will be reported to the UMMS PI and project coordinator who will report it to the appropriate authority.

There will be bi-weekly telephone meetings involving study staff from all recruitment locations. Core study staff (PIs and Directors/Coordinators) of all locations will meet weekly. Meeting minutes will be emailed to study staff and stored in a location all study staff can access.

19) **Community-Based Participatory Research***

N/A

20) **Sharing of Results with Subjects***

Currently, there are no plans to share results with subjects.

21) **Setting**

The Take a Break research study will be conducted at the UMass Memorial Health Care, led by research staff within the Quantitative Health Sciences (QHS) Department, and external sites including Northwell Health, VACWM and RMG. Please note that as of June 2019, Northwell Health is no longer actively recruiting study participants. All sites will follow the protocol as specified in this ISP. Additionally, Northwell Health and VACWM have ISPs which mirror this ISP and are approved by their own IRBs. UMMS study staff may provide assistance in recruitment at external study sites after receiving required approval at each site.

UMMS Division of Health Informatics and Implementation Sciences (HIIS):

Within QHS, HIIS houses the Biomedical Research Informatics Development Group (BRIDG), and the Technology Usability lab.

- UMMS Biomedical Research Informatics Development Group (BRIDG): The BRIDG (Rajani Sadasivam, PhD, Director) provides informatics consultation and application development support for UMMS researchers. The BRIDG has expertise in the development and evaluation of provider and patient facing e-health technologies. The BRIDG also closely works with the Quantitative Methods Core for data management. The BRIDG will be responsible for the refinement of the Take a Break apps.
- Technology Usability Lab (Rajani Sadasivam, PhD, Director): The lab is a state-of-the-art facility designed to support multiple types of usability studies which utilize video and audio recordings. The two-room suite is designed to accommodate focus groups, as well as individual and multi-user evaluation sessions. The lab has a testing room and an adjacent observation room with capacity for 5 observers. The two rooms are separated by a one-way mirror to allow study personnel to observe the test sessions. The testing room is equipped with 6 computers that have the Morae usability "Recorder" software configured on them. The Morae "Recorder" allows for live capture of subject being tested including recording of clicks, keystrokes, and other events. Each of these computers can be observed using two computers in the observation room that have the Morae "observer" software installed on them. The lab offers a wide range of viewing angles and auxiliary macro cameras for ultimate flexibility in product testing, for both software and physical devices. The lab also supports recording of other types of user testing (focus groups, interviews, exergaming etc.) through five high definition cameras installed on the four sides and the center wall of the room. The video and audio of all of these cameras are securely captured using state-of-the-art video and audio recording equipment. In

addition, the usability lab also has a 5N inch LCD television through which training sessions and demonstrations can be conducted. All usability testing will take place in the Usability Lab.

- The research project offices where the study will be conducted are on the University's computer network which has extensive mainframe and microcomputer facilities and capacities. Each of these is equipped with a high-speed personal computer using shared storage on the UMMS network where it is backed up daily. Faculty offices and conference rooms within the division located on the 8th floor of the Albert Sherman Center will be used for sessions with the tobacco treatment specialist and for conducting smoking cessation verification.

Northwell Health:

Northwell Health is the largest clinically integrated healthcare network in New York State and the third largest non-secular health care system in the United States. Northwell Health consists of 21 owned and affiliated hospitals and employs 2,700 physicians and 15,000 nurses serving a catchment population of 8 million people. There are 450 ambulatory and physician practices with more than 5,000 support staff. The research infrastructure for Northwell Health is the Feinstein Institute for Medical Research. The Feinstein Institute for Medical Research is located on the campus of North Shore University Hospital but clinical research extends throughout the Health System. The Feinstein supports two centralized health system IRBs and a Grants Management Office for pre- and post-award services. These facilities and services are available to all faculty of the health system.

Patient recruitment will be conducted in ambulatory primary care practices under the Division of General Internal Medicine. The Division of General Internal Medicine is composed of a large, dynamic, and diverse group of clinicians, educators, and researchers who provide comprehensive primary care services. The Division also provides preventive care with a particular emphasis on managing chronic conditions such as hypertension, diabetes, and cardiovascular disease. There is also an emphasis on continuity of care, preventive medicine, and patient education. The Division has implemented several disease management interventions for depression, addictions, and medication adherence.

The Division's largest practice in Great Neck, NY includes both a faculty and resident practice with approximately 32,000 visits per year. Patients from a variety of socioeconomic and ethnic backgrounds are cared for by 16 faculty providers and 72 internal medicine residents. In addition to medical staff the practice includes a clinical psychologist, 2 nurse practitioners, 2 social workers, a certified diabetes educator, a clinical pharmacist, and a nutritionist. Medical assistants, nurses, and administrative staff support clinical staff members.

VA Central Western MA:

VACWM provides primary, specialty, and mental health care, including psychiatric, substance abuse and PTSD services, to a Veteran population in central and western Massachusetts of more than 120,000 men and women. Care is provided at the Northampton VA Medical Center, which has 85 behavioral health beds, a 44-bed nursing home care unit, and a 16-bed substance abuse, compensated work therapy and transitional residence located off-campus. The healthcare system also oversees seven community-based outpatient clinics (CBOCs) in Fitchburg, Greenfield, Pittsfield, Springfield, and 3 clinics in Worcester.

VACWM is an increasingly dynamic and growing research program that focuses on developing and studying innovative methods to improve quality, efficiency and access of care to Veterans around the

country. As part of its commitment to increasing availability and study of Veterans' healthcare, new clinics have been built for specialty services and research in Worcester, MA. This will be the primary recruitment site for this project at VACWM. The Worcester Plantation Clinic is located within a newly constructed UMass Medical School (UMMS) building and is located across the street from UMMS main campus. As a result, VACWM maintains strong academic affiliations for teaching and research with the University of Massachusetts Medical School in Worcester. Thus, VACWM is an intellectually rich environment with a wide range of expertise available to inform the successful completion of this project.

Reliant Medical Group**:**

The study will be conducted in the context of a large multi-specialty group practice (Reliant Medical Group) located in Central Massachusetts, which has proven to be an ideal setting for conducting a number of prior NIH and AHRQ-funded studies focused on improving medication safety and health outcomes, as well as falls in the elderly. In addition, Reliant was a center for the Women's Health Initiative, as well as a major Mammography Study.

Reliant Medical Group employs 265 physicians and 80 mid-level providers, and provides care for over 252,000 patients at 20 office locations across Central Massachusetts. The practice has used an EHR since 2006 (Epic Systems Corporation). Epic's EHR, EpicCare®, is ARRA certified by the Certification Commission for Health Information Technology (CCHIT). Recruitment and verbal consent will take place via telephone at Reliant Medical Group offices in Worcester, MA. The in-person intervention and consent process will take place at RMG Pulmonary Department located at Worcester Medical Center (123 Summer Street), telephone visits will also take place with a Reliant Tobacco Treatment Specialist (whose main office is in Webster, MA). Data collection/analysis will take place at Reliant Medical Group and UMass Medical School in Worcester, MA.

22) **Resources Available**

The Department of Quantitative Health Sciences' (QHS) mission is: (a) to fulfill the quantitative health science needs of the academic medical center to become a leader in clinical and translational research; (b) to weave service to the academic medical center into discovery of new approaches to address the health care needs of the Nation; and (c) to train the next generation of scientists who will contribute to the health of populations and individuals and the transformation of health care through methodological innovation. The research team is part of the UMMS Division of Health Informatics and Implementation Sciences (HIIS). The research vision for the Division is to create new knowledge focusing on computational, cognitive, and socio-cultural aspects of health informatics. The Division of HIIS works closely with Northwell Health, VACWM and RMG systems. Consistent with the vision of the division, and driven by institutional needs, HIIS faculty have been recruited with expertise in clinical research informatics, consumer health informatics, human factors and human-computer interaction, clinical decision support, data mining and natural language processing. The Division houses nine faculty, program directors, and programmers.

Core Investigative Team:

- Principal Investigator: The PI is currently a Professor at the University of Massachusetts Medical School and Director of the Division of Health Informatics and Implementation Science. While still an active clinician at the Bedford VA, they devote their time at UMass to research and directing the research mission of the division. They also have secondary appointments in the UMass Division of Preventive Medicine. The PI has gained national recognition for their health informatics research with

a specific focus on patient informatics. They have been PI of two NIH-funded R01 tobacco control grants (R01DA017971 and R01CA129091). They have published articles on tobacco epidemiology, health services delivery, research methods, and intervention to reduce tobacco use. In concert with their other colleagues in primary care, the PI will review eligibility and enrollment of patients (including appropriateness of NRT). The PI will be responsible for the overall conduct of the study.

- Co-Investigator: The Co-Investigator has over past 15 years of continuous extra-mural funding from the National Institutes of Health, the Agency for Healthcare Research and Quality, and the Robert Wood Johnson Foundation. They initially trained as a primary care physician and epidemiologist, and for the past ten years, has had a career focused on implementation science and health disparities research. They are the Vice Chair of QHS, and also directs the NIH-funded Center of Health Equity Intervention Research (CHEIR). Since we anticipate a high percentage of lower income and minority patients, the Co-Investigator was recruited to the team. They will lend their expertise to the project by being involved in the implementation planning of the study, and consultant on the analysis of study data.
- Co-Investigator: The Co-Investigator is an Assistant Professor in the Division of Health Informatics, QHS. They are also trained as a Tobacco Treatment Specialist. They are a recent awardee of a K07 award entitled "Smoker for Smoker (S4S)," designed to train in cancer health behavior, health communication, intervention design, and analysis. The Take a Break project is in direct alignment with these goals, and their efforts will be concurrent. Under the direction of the PI, they will advise on the refinement of the interactive mHealth tools, and assist in supervision of the programmer. They will also provide expertise in usability assessment.
- Co-Investigator: The Co-Investigator has successfully implemented Electronic Health Records and has also worked to upgrade and maintain those systems. Their research focuses heavily on user workflows and strives to implement informatics solutions that maximize the efficiency of health care providers. They are an expert in retrieving data from outpatient clinical systems and turning into actionable data to improve quality of care. They will work to develop the recruitment protocols, and data extraction through the Allscripts EHR at UMass. The co-investigator has a primary appointment at the University of Alabama but remains an adjunct faculty member at UMMS. There is an IRB authorization agreement in place for the University of Alabama to defer to UMMS as the IRB of record.
- Biostatistician: The Biostatistician is a senior faculty member of the Quantitative Methods Core, who will direct the statistical analyses for evaluating processes and outcomes.
- Investigator: This Investigator has extensive experience in tobacco dependence treatment in their role in oversight of the tobacco and smoke-free campus movement for both UMass Memorial Health Care and the University of Massachusetts Medical School. They will provide input in the implementation of the study intervention and assist with recruitment. They will work closely with the consultants in developing and implementing the in person and telephone contact with smokers.
- Project Director: The PD will be responsible for overseeing the recruitment of patients to participate in the study, and conducting the planning visit with participant pre-break. They will work with the Research Assistants in other aspects of implementation of the study protocol, oversee distribution of incentives to participants, and will direct the research assistants in any other needed areas.
- Project Coordinators: The Project Coordinators, under the direction of the project director, will participate in all phases of patient recruitment, patient telephone follow-up, and conduction of the

study and wrap up of the study but will specifically coordinate patient follow-up. They will work closely with project personnel to design and print materials required for the project.

- Research Assistants: The Research Assistants will be responsible for preparing and assembling all materials for the study. They will prepare all IRB and human use protocol materials, ensuring annual renewal of IRB. They will assist in the production of study materials, assist with recruitment, participant visits, and conduct follow-up calls as needed.
- Website Programmer: The Website Programmer, under the direction of the Co-Investigators, will be responsible for developing the elements of the interactive internet intervention including Active Server Pages and HTML coding, database design, login and security of the program and data, and development of the control program.
- CONSULTANTS:
  - A trained TTS Consultant will work with the Investigator to recruit patients and conduct assessment at 1 week.
  - An additional consultant is Associate Professor in the Department of Psychiatry at the Medical University of South Carolina and will advise us on the implementation of the intervention process.
- RMG Study Team
  - Site-PI: The RMG site PI will be responsible for conducting all research-related procedures at RMG and will participate in bi-weekly telephone meetings with UMMS study staff.
  - Project Coordinator: The project coordinator, under the direction of the Research Manager, will participate in all phases of patient recruitment, patient telephone follow-up, and conducting all study activities at RMG.
  - Research Manager: The research manager will be responsible for overseeing the day-to-day study activities and implementation of the study protocol and supervision of project coordinator.
  - Tobacco Treatment Specialist (TTS): The RMG TTS will be responsible for conducting the 1-week telephone visit for all RMG participants.
  - Programmer/Analyst: The programmer/analyst will be responsible for generating the SMART alert in the EHR.
- Northwell Health and VACWM site PI/PD: The Northwell Health and VACWM site PI's will be responsible for conducting all research-related procedures at each corresponding site. They will oversee all elements of recruitment at each sites. To ensure that all persons assisting with the research are adequately informed about the protocol, the research procedures, and their duties and functions, all site PI's and research team will participate in bi-weekly telephone meetings with UMMS study staff to provide any updates. All -site PI/PD's will also meet weekly with the UMMS PI (or their designee) and PD to discuss any issues or concerns with recruitment. Meeting minutes

will be drafted by a UMMS research assistant/coordinator and will be emailed to all study staff and stored in a location that all study staff can access.

UMMS study personnel may assist performing research activities at Northwell Health, VACWM and RMG sites as approved by each study site. Northwell Health, VACWM and RMG study personnel will not perform research activities at UMMS.

Smoking Cessation verification equipment (CO meters), Nicotine Replacement Therapy (NRT), and up to 100 smart phones will be purchased throughout the study.

23) **Prior Approvals**

Approvals from Northwell Health and VACWM IRB have been obtained prior to start of any research activities. RMG Research Department has granted approval for research to take place with UMMS IRB approval.

24) **Recruitment Methods**

See section 7: Study-Wide Recruitment Methods

Compensation: The schedule of participant compensation is shown below. All compensation will be received within 48 hours upon completion of the particular task (i.e. after in-person session, after telephone survey). Compensation will be in the form of Amazon gift cards, in $25 and $50 denominations .Study participants at RMG will receive checks (mail to them after each visit) in the same amounts as Amazon gift cards.

Table 5: Compensation Type for each Study Aim/Task

Research Method	Participants	Duration	Honoraria (All in the form of Amazon gift cards and checks)
Aim 1 Usability Testing	Smokers from UMass Clinics and Inpatient	1 hour	In-person visits $50 each; 1 in-person visit
Aim 1 Mini Pilot	Smokers from UMass Clinics and Inpatient	3 weeks	Two in-person visits are $50 each; two phone contacts are $25 each – total of $150 /participant
Aim 2 Take a Break Intervention	Smokers from UMMS, Northwell Health, VACWM and RMG	3 weeks	Three in-person visits are $50 each; one phone contact is $25 – total of $175 participant
Aim 3 Follow-Up	Smokers from UMMS, Northwell Health, VACWM and RMG	6 months	
Quality Improvement Interviews	UMMHC Nurses & hospital leadership	45 minutes	$50 per interview

25) **Local Number of Subjects**

For Aim 1 usability testing, we will recruit up to 20 local subjects. For the Aim 1 mini pilot, we will recruit up to an additional 30 local participants. We will recruit up to 300 participants locally for the RCT (Aim 2 &3).

26) **Confidentiality**

We have stringent protection against breach of confidentiality using secured servers and locked office spaces for data entry at each site. The research team at each site will do periodic checks to ensure that participant confidentiality is protected at all stages of data management and analysis. At the start of the evaluation all project team members will be trained in practices that ensure participants' confidentiality and privacy.

Recordings collected during usability testing will be de-identified using subject ID numbers. No identifiable information, such as a full name or image of a subject's face, will be collected by the recording. Identifiers will be collected separately and will be stored in an encrypted form. Recordings will be transcribed and de-identified. Recordings will be stored in a secured UMMS drive specified for the study within the UMMS IS regulated environment, where only UMMS study staff will have access to them. Recordings, and all other data collected in this study, will be retained and destroyed in accordance with SOP HRP-800.

All data will be stored in a HIPAA compliant regulated environment and access will be only through a secure VPN network. All patient related identifiers are encrypted in the database. The investigators have substantial experience with implementing these methods successfully in their research. All data will remain confidential and only reported in aggregate. UMMS will have access to Northwell Health, VACWM and RMG recruitment data. All data collected through the RCT will be stored in REDCap and our secure mHealth system. All in-person session (UMMS, Northwell Health, VACWM and RMG) data collection will be conducted using paper forms. Paper forms will be stored in a locked office within a locked cabinet at each study site. All data from paper forms will be entered into REDCap, which is hosted in our regulated environment and all data collected through it is stored in the UMMS regulated database servers.

All subjects, for all study aims, will be assigned an ID number and a link between the ID number and identifiable information will be stored and secured in a different drive folder than any study data.

For participants using their own personal smart phones, all security precautions will be taken to prevent access to app usage data. This data will be encrypted using industry standard encryption algorithms. Additionally, we will support remote-wipe capabilities in the event a phone is stolen or lost.

All data for patients who were screened for participation but did not consent to participate in the study, will be destroyed once recruitment has been completed for Aim 2.

27) **Provisions to Protect the Privacy Interests of Subjects (HIPAA)**

We have minimized data collection to only what is needed to answer our hypotheses. We have stringent protection against breach of confidentiality using secured servers and locked office spaces for data entry at UMMS. The research team will do periodic checks to ensure that participant confidentiality is protected at

all stages of data management and analysis. At the start of the evaluation all project team members will be trained in practices that ensure participants' confidentiality and privacy.

We are requesting a waiver of HIPAA authorization, (see *HIPAAwaiver-TAB_21815*). Recruitment cannot be undertaken using health information that has been de-identified. It is not feasible for the research team to obtain a signed Authorization for all PHI that we need to obtain for recruitment. Consent to participate in the usability testing, mini pilot, and RCT will be written. We will protect all patient information by keeping all data of enrolled participants on a secure UMMS server, on a separate drive specified for the evaluation, behind the UMMS firewall. All data files will be labeled with a participant code unrelated to any participant information. UMMS will maintain a master list of participants and linked codes, but these will be stored separately from the data and accessible only by select research staff. Each file will have a site level and participant level code.

Additionally, we are requesting a HIPAA Authorization to use PHI for research purposes. Attached to the eIRB is a HIPAA Authorization form that will be presented at the time of consent. We will be using demographics and medical diagnosis within analysis. If a participant does not sign the authorization form, we will not use the PHI obtained for recruitment for research purposes. Therefore, we will not be using the PHI of anyone who is not a participant in the study and who did not sign an authorization form. We believe by using the PHI already obtained, we are reducing the burden on the participant by limiting the amount of data collection they are directly involved in.

28) **Compensation for Research-Related Injury**

This research does not involve more than minimal risks to participants. Consequently, no funds have been set aside for research-injury compensation.

29) **Economic Burden to Subjects**

We will provide smartphones and cellular access to smokers who do not have access to one. We will also compensate travel costs.

30) **Consent Process**

We will be obtaining consent for participation in this study in accordance with HRP-802. The process of informed consent will begin before the intervention is administered or any data (not including EHR data) is collected (see table 6 for type of consent). The study procedures will be explained prior to consent. Participants will be given the opportunity to ask any questions or for clarifications before consenting to participation. It will be explained that the healthcare they receive at UMMHC or Northwell Health or VACWM or RMG will not be affected by their decision to participate or to not participate in the study. Participants will then read the consent form and sign it (see Consent Form A1a, Consent Form A1b, Consent Form A1c, and Consent Form 2 & 3), if they choose to participate. Participants may opt out of the research study at any time. If necessary, all participants will be given additional information throughout the course of the study in order to maintain informed consent.

Table 6: Consent Type for each Study Aim

Research Method	Participants	Duration	Number	Consent
Aim 1 Think Aloud Usability	Smokers from UMass Clinics and Inpatient	1 hour	20	Written
Aim 1 Mini Pilot(s)	Smokers from UMass Clinics and Inpatient	3 weeks	30	Written
Aim 2 Take a Break Intervention	Smokers from UMMS, Northwell Health, VACWM and RMG	3 weeks	500	Written
Aim 3 Follow-Up	Smokers from UMMS, Northwell Health VACWM and RMG	6 months	500	Written
QI interviews	UMMHC Nurses & hospital leadership	45 minutes	30	Verbal

Individuals that are non-English speaking, not yet adults (infants, children, teenagers), cognitively impaired, or are unable to consent will be excluded from participating in the study.

Waiver or Alteration of the Consent Process: We are requesting a waiver of HIPAA authorization (see UMass HIPAA Waiver Appendix) for recruitment purposes.

For the quality improvement interviews, we will explain study procedures prior to obtaining verbal consent. Participants will be given the opportunity to ask any questions or for clarifications before verbally consenting to participation. Upon verbal consent, the participant will receive a Fact Sheet that summarizes the study for their records.

31) **Process to Document Consent in Writing**

Since all of our study aims will only include written consent (see Table 6), we will be following the guidelines to obtaining written consent outlines in SOP: Written Documentation of Consent (HRP-803).

We will:

- Verify that the consent form is in language understandable to the participant
- Print the name of the following individuals on the consent document:
  - Subject/Representative
  - Person obtaining consent
- Have the following individuals personally sign and date the consent document:
  - Subject/Representative
  - Person obtaining consent
- Provide copies of the signed and dated consent document to the subject/representative

We request a Waiver of Documentation of Consent for the quality improvement interviews. The interviews involve no more than Minimal Risk to the participants. The procedures in place to protect patient confidentially are described in sections 11, 26 and 27. The waiver will not adversely affect the rights and welfare of the subjects. Whenever appropriate, the participants will be provided with additional pertinent information after participation. In the unlikely event of this happening, we will contact UMMS IRB for guidance. This evaluation meets the following criteria for a waiver of written documentation of the consent process for the subsequent reasons:

• The evaluation presents no more than Minimal Risk of harm to subjects.
• The evaluation involves no procedures for which written consent is normally required outside the research context.

32) **Drugs or Devices**

The NRT used in this study is not investigational, and therefore, does not have an IND. The NRT being used in this study is IND exempt since it meets the following criteria: 1) The drug is lawfully marketed in the United States; 2) The investigation does not involve a route, dosage level, or use in a patient population or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product; 3) The investigation is not intended to be reported to FDA as a well-controlled study in support of a new indication for use nor intended to be used to support any other significant change in the labeling for the drug; and 4) The investigation is not intended to support a significant change in the advertising for the product.

The lozenges will be stored according to the instructions on the box. They will be locked up inside the PI/PI-designee's office. Only IRB-approved members of the research team, Tobacco Treatment Specialists or physicians will provide NRT to the participants. Participants will be asked about any FDA contraindications at the time of dispersion. For all sites, the lozenges will be purchased by UMMS from a commercial vendor and mailed to each site as required. For Northwell Health and RMG, the lozenges will be kept locked in the site-PI-designee's office. For VACWM, the lozenges will be stored according to the instructions on the box and will be kept at the VACWM pharmacy. Only physicians listed as study staff will be able to prescribe NRT to the participants. Additionally, a copy of the participant's informed consent form will be uploaded to the participant's electronic medical record prior to dispensation of NRT.

Participants can choose to use or not to use the NRT. It will be provided to participants, but use of it is optional. A dispensation log will be kept at each site detailing the NRT that was provided to participants and the research staff member dispensing the lozenges. If participants use the NRT, they will be asked to participate in a smoking cessation verification test using a carbon monoxide (CO) monitor. At the conclusion of the project, unused NRT will be returned to study staff at UMMS for proper disposal if desired by participants. All returned NRT will be destroyed by the UMMS IDS pharmacy.

33) **References**

1. Danaei G, Ding EL, Mozaffarian D, et al. The preventable causes of death in the United States: comparative risk assessment of dietary, lifestyle, and metabolic risk factors. PLoS medicine. Apr 28 2009;6(4):e100058.
2. Fiore M, Bailey, WC, Cohen, S, et.al. . Treating Tobacco Use and Dependence: Clinical Practice Guideline 2008 Update. US Department of Health and Human Service, Public Health Service, Agency for Health Care Policy and Research. 2008(208):37.
3. Carpenter MJ, Hughes JR, Solomon LJ, Callas PW. Both smoking reduction with nicotine replacement therapy and motivational advice increase future cessation among smokers unmotivated to quit. J Consult Clin Psychol. Jun 2004;72(3):371-381.
4. Baker TB, Mermelstein R, Collins LM, et al. New methods for tobacco dependence treatment research. Annals of behavioral medicine : a publication of the Society of Behavioral Medicine. Apr 2011;41(2):192-207.
5. Schlam TR, Baker TB. Interventions for tobacco smoking. Annu Rev Clin Psychol. 2013;9:675-702.
6. Piper ME, Baker TB, Mermelstein R, et al. Recruiting and engaging smokers in treatment in a primary care setting: developing a chronic care model implemented through a modified electronic health record. Translational behavioral medicine. Sep 2013;3(3):253-263.

7. Moore D, Aveyard P, Connock M, Wang D, Fry-Smith A, Barton P. Effectiveness and safety of nicotine replacement therapy assisted reduction to stop smoking: systematic review and meta-analysis. Bmj. 2009;338:b1024.
8. Carpenter MJ, Hughes JR, Gray KM, Wahlquist AE, Saladin ME, Alberg AJ. Nicotine therapy sampling to induce quit attempts among smokers unmotivated to quit: a randomized clinical trial. Arch Intern Med. Nov 28 2011;171(21):1901-1907.
9. Burris JL, Heckman BW, Mathew AR, Carpenter MJ. A Mechanistic Test of Nicotine Replacement Therapy Sampling for Smoking Cessation Induction. Psychol Addict Behav. Oct 27 2014.
10. Jardin BF, Cropsey KL, Wahlquist AE, et al. Evaluating the effect of access to free medication to quit smoking: a clinical trial testing the role of motivation. Nicotine Tob Res. Jul 2014;16(7):992-999.
11. Bandura A. Health promotion by social cognitive means. Health education & behavior : the official publication of the Society for Public Health Education. Apr 2004;31(2):143-164.
12. Bandura A. Self-efficacy : the exercise of control. New York: W.H. Freeman; 1997.
13. Bandura A. Self-efficacy: toward a unifying theory of behavioral change. Psychol Rev. Mar 1977;84(2):191-215.
14. Baranowski T, Perry C, Parcel G. How Individuals, Environments, and Health Behavior Interact. In: Glanz K, Lewis F, Rimer BK, eds. Health Behavior and Health Education. Second ed. San Francisco: Jossey-Bass; 1997:153-178.
15. Kushniruk AW. Analysis of complex decision-making processes in health care: cognitive approaches to health informatics. Journal of biomedical informatics. Oct 2001;34(5):365-376.
16. Kushniruk AW, Patel VL. Cognitive computer-based video analysis: its application in assessing the usability of medical systems. Medinfo. 1995;8 Pt 2:1566-1569.
17. Ancker JS, Carpenter KM, Greene P, et al. Peer-to-peer communication, cancer prevention, and the internet. Journal of health communication. 2009;14 Suppl 1:38-46.
18. Sadasivam RS, Chan WS, Balakrishnan K, et al. Crave-Out! A Smartphone Game to Prevent Relapse after Quitting Smoking. Paper presented at: Medicine 2.0 2012; Boston, MA.
19. Kamberi A, Delaughter K, Sadasivam RS, Houston TK. Crave-Out! A game for Distraction of cigarette cravings. Paper presented at: Society of Behavioral Medicine Annual Meeting 2014; Philadelphia, PA.
20. Fiore M, Jaen C, Baker T, et al. Treating Tobacco Use and Dependence: 2008 Update. Clinical Practice Guideline. Rockville, MD: U.S. Department of Health and Human Services. Public Health Service; May2008.
21. McClernon FJ, Westman EC, Rose JE. The effects of controlled deep breathing on smoking withdrawal symptoms in dependent smokers. Addictive Behaviors. 6// 2004;29(4):765-772.
22. Houston TK, Sadasivam RS, Ford DE, Richman J, Ray MN, Allison JJ. The QUIT-PRIMO provider-patient Internet-delivered smoking cessation referral intervention: a cluster-randomized comparative effectiveness trial: study protocol. Implement Sci. 2010;5:87.
23. Houston TK, Richman JS, Ray MN, et al. Internet delivered support for tobacco control in dental practice: randomized controlled trial. J Med Internet Res. 2008;10(5):e38.
24. Sadasivam RS, Delaughter K, Crenshaw K, et al. Development of an interactive, Web-delivered system to increase provider-patient engagement in smoking cessation. J Med Internet Res. 2011;13(4):e87.
25. Houston TK, Coley HL, Sadasivam RS, et al. Impact of content-specific email reminders on provider participation in an online intervention: a dental PBRN study. Stud Health Technol Inform. 2010;160(Pt 2):801-805.
26. Houston TK, Ford DE, Sadasivam RS, et al. Overcoming limits to tobacco control: using the internet to bridge clinical and public health interventions. AMIA Annu Symp Proc. 2008:977.
27. Bandura A. Social Foundations of Thought and Action: a social cognitive theory. Englewood Cliffs, NJ: Prentice Hall; 1986.
28. Velicer WF, Diclemente CC, Rossi JS, Prochaska JO. Relapse situations and self-efficacy: an integrative model. Addict Behav. 1990;15(3):271-283.
29. Brown R, Burgess E, Sales S, Whiteley J, Evans D, Miller I. Reliability and validity of a smoking timeline follow-back interview. Psychology of Addictive Behaviors. 1998;12(2):101-112.
30. West R, Hajek P, Stead L, Stapleton J. Outcome criteria in smoking cessation trials: proposal for a common standard. Addiction. Mar 2005;100(3):299-303.

31. Hughes JR, Keely JP, Niaura RS, Ossip-Klein DJ, Richmond RL, Swan GE. Measures of abstinence in clinical trials: issues and recommendations. Nicotine Tob Res. Feb 2003;5(1):13-25.
32. Austin PC, Manca A, Zwarenstein M, Juurlink DN, Stanbrook MB. A substantial and confusing variation exists in handling of baseline covariates in randomized controlled trials: a review of trials published in leading medical journals. J Clin Epidemiol. Feb 2010;63(2):142-153.
33. Senn S. Testing for baseline balance in clinical trials. Statistics in medicine. Sep 15 1994;13(17):1715-1726.
34. MacKinnon DP. Introduction to statistical mediation analysis. New York: Lawrence Erlbaum Associates; 2008.
35. Hintze J. PASS 11. 2011; www.ncss.com.