Study Protocol (including Statistical Analysis Plan (SAP))

Official Title: mHealth Messaging to Motivate Quitline Use and Quitting (M2Q2): RCT in rural Vietnam

NCT#: NCT03567993

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INVESTIGATOR STUDY PLAN - REQUIRED

1. TITLE:

mHealth Messaging to Motivate Quitline Use and Quitting (M2Q2)

2. EXTERNAL IRB REVIEW HISTORY*

This study has been reviewed by the IRB at the Institute for Population, Health and Development (PHAD) in Hanoi, Vietnam. The information contained in this ISP is parallel to the information submitted to the IRB at PHAD. All revisions to this ISP will be sent to the PHAD IRB after obtaining approval from the UMMS IRB.

Please note: all contact, including consent, interviews, and all study procedures with human subjects will occur onsite in Vietnam. All data will be collected by PHAD investigators and staff under sub-award from UMMS. All data will be de-identified according to HIPAA standards prior to transfer to UMMS investigators and staff. Therefore, UMMS investigators and staff will provide scientific direction only and will have no contact with human subjects.

3. PRIOR APPROVALS:

N/A

Conflict of Interest (COI):

N/A

Clinical Engineering Department:

N/A

Biohazardous Agents:

N/A

Radiation*:*

N/A

4. OBJECTIVES*

We propose the following Specific Aims:

Specific Aim 1: In collaboration with the Institute of Population, Health, and Development (PHAD) in Hanoi Vietnam, we will adapt our current, effective texting system to Vietnam. The texting system will: Motivate smokers to quit smoking, using tailored messages adapted to be culturally relevant. Encourage smokers to accept counseling services from the quitline, and take advantage of no-cost NRT that will be provided by the quitline to those willing to quit.

Specific Aim 2: Engage with the Bach Mai quitline, providing additional training in tobacco cessation counseling for those ready to quit, and motivational interventions for those not yet ready to quit.

Specific Aim 3: In a randomized trial (N = 600 men and women smokers in the Red River Delta), evaluate the impact of the texting system on access to the quitline, use of nicotine replacement therapy, increase in self-efficacy, and six-month biochemically verified smoking cessation. A qualitative interview will be completed with a sub-sample of these participants (N = 30) after the six-month follow-up survey is complete.

Our primary hypothesis is that smokers in the M2Q2 intervention will have higher rates of smoking cessation, compared with the comparison group.

5. BACKGROUND*

Smoking is a leading preventable cause of mortality internationally. Effective aids to smoking cessation are available.[1] The use of pharmacological cessation aids combined with behavioral counseling doubles the chances of successfully achieving long-term cessation,[1] but these treatments are often underutilized, especially in low and middle income countries where rates of tobacco use are quite high, particularly in rural areas. In this project, we will work with the Vietnam government agencies (Ministry of Health), the Vietnam Respiratory Society, scientists with expertise in tobacco control and mobile health, local community clinical services in rural areas, and a newly established telephone “quitline” service to engage and motivate harder-to-reach rural Vietnamese men and women to quit smoking cigarettes.

In Vietnam, 47.4% of men and 1.4% of women smoke, based on the 2010 Global Adult Tobacco Survey (non-institutionalized men and women aged 15 years or older (N=9,925)). Rates were even higher in rural areas of Vietnam. In another national survey in Vietnam (N=14,706), the majority of smokers (70.5%) were between the ages of 55 and 64.[2] The median age in which Vietnamese men and women first started smoking was 19 and 20 years of age, respectively. The median amount of cigarettes smoked per day for both sexes was 6. Due to the high prevalence of smoking in men, we anticipate the majority of our sample will be Vietnamese men, but plan to recruit women into the study as well. Further, only 24.4% of smokers have used nicotine replacement therapy, patch or chewing gum and 0.4% have used prescription medication to try and stop smoking.[3] Only 2.7% of smokers attempting to quit in Vietnam report receiving counseling.[3] Further, most smokers in rural Vietnam are thinking of quitting, but not ready to quit in the next month. Thus, these smokers need motivational support,[4, 5] and encouragement to use counseling (such as telephone quitline services) and treatments (nicotine replacement therapy).

Vietnam ratified the World Health Organization Framework Convention on Tobacco Control in 2004 and it was updated in 2014. Vietnam has made great strides in

establishing policies to support tobacco control, including banning sales to minors, having pictogram health warnings occupy over 50% of tobacco packaging, and establishing a comprehensive ban on all tobacco advertising.

Recently, Vietnam has begun to initiate quitline services. In September 2015, a quitline was established in Bach Mai hospital in Hanoi (northern Vietnam) by the Vietnam Respiratory Society. The quitline was funded by the Vietnamese Ministry of Health through their Tobacco Control Fund. The fund was established by the Prime Minister of Vietnam in 2013 and collects all revenue from taxes on tobacco products. It's current priority goals are to provide information, education, and communication (IEC) on tobacco harm, develop and implement smoke-free programs in communities, and establish quitline services.

Over the past 6 months, the Bach Mai quitline has been called, on average 25 times per day. Quitline tobacco treatment specialists are registered nurses or public health professionals who have been trained in principles of motivational interviewing, evidence for risk of tobacco, benefits of quitline, and strategies summarized in the 2008 U.S. Treating Tobacco Use and Dependence guidelines (including "5As" and 5Rs". The "5 As" include: Ask, Advise, Assess, Assist, and Arrange.[6] The "5 Rs" (Relevance, Risks, Rewards, Roadblocks, and Repetition) are helpful in motivating a smoker to quit. Quitline counselors are trained in motivational interviewing techniques.[7] At the end of training, counselors are certified as Tobacco Treatment Specialists and obtain a certificate issued by the Bach Mai hospital smoking cessation program. Currently, Nicotine Replacement Therapy is provided for smokers at no cost, funded by the Tobacco Control Fund dollars.

As further detailed below, conversations with the Vietnam Ministry of Health, Institute of Population, Health, and Development (PHAD), the new quitline in Bach Mai, and our prior work with local Vietnamese community clinics have guided our proposed intervention strategies.

In the U.S., as in Vietnam, the majority of smokers are not actively quitting at any given time.[8] Historically, less interventional work has focused on these smokers compared to smokers are who ready to quit. We have developed automated motivational messaging systems to support smoking cessation, and a recent trial with 900 U.S. smokers demonstrated that the system is effective both for smokers ready to quit and for those not ready to quit. In this project, we propose to adapt this system for texting rural Vietnamese male and female cigarette smokers, with two mobile health goals: Motivating smokers to quit smoking, using tailored messages adapted to be culturally relevant and encouraging smokers to accept counseling services from the quitline, and take advantage of no-cost NRT that will be provided to those willing to quit.

As this is a population in need of engagement and motivation, we propose to engage patients through their local community clinical services to use a mobile health intervention (automated texting system) that will be culturally adapted to Vietnam with

messages written by Vietnamese smokers, and motivate access to the Bach Mai quitline. Below, we provide more details on the significance of these two goals in Vietnam.

Goal 1: Motivating smokers to quit smoking texting system

M2Q2 Motivational Messaging system: Over the last 6 years, our team has continued to develop and evaluate a tailored motivational messaging system (R21-CA089011, 1R01CA129091-01).[9-12] Conceptually, the message strategies were designed around the core constructs from Social Cognitive Theory including enhancing self-efficacy.[13] Self-efficacy has been defined as the perceived capacity to perform a behavior.[14, 15] Self-efficacy can influence outcome expectations, the estimation that a given behavior will lead to a certain outcome. A key development effort was the authoring of over 600 motivational messages, including 500 written by experts, and a set of 100 messages written by smokers for smokers,[16] all tailored to readiness to quit. Expert-written messages were developed iteratively through a group review, and the content was guided by current guidelines[17] and Social Cognitive Theory.[18] Smoker-written messages were written by current smokers responding to scenarios that varied on readiness to quit smoking. In testing these messages in our prior NIH-funded trials, we have demonstrated that the messages have two effects:

The messages increased engagement (participation) in the online smoking intervention. The messages increased six-month smoking cessation outcomes. Compared to non-message days, engagement in the online smoking intervention was most likely to occur on 3 days surrounding the motivational message (OR=5.4, 95% CI=4.02-7.31). The peer messages were even more potent in increasing engagement. Smoker 2 Smoker messages were twice as likely to generate new activity in the online smoking intervention (OR=2.03, CI=1.74-2.35), compared with the expert-written messages.[16] This effect remained after adjusting for time from registration and smoker characteristics.

We recently completed a randomized trial among 900 active smokers referred by clinics across all regions of the United States. After six months of follow-up, smokers who received the motivational messages were more likely to quit smoking compared with smokers who received an interactive website but not the motivational messages (Odds Ratio 1.7 (95% CI 1.03-2.81)).

As noted, the motivational messaging system is tailored to readiness to quit, with separate messages designed for those ready to quit, and those not ready to quit. In our NCI-funded trial (R01-CA-129091)[11] involving those ready to quit and those not ready to quit, the messages were similarly effective in Motivation Phase (6-month cessation 23% versus 15% control) and Pre-cessation Phase smokers (37% versus 24% control). Interventions for smokers need to be more accessible.[19] We are currently using this system to deliver messages through texting to an additional sample of smokers who are

specifically recruited because they are not ready to quit (TAB 1R01CA190866-01). We plan to adapt this texting system for Vietnam, and have smokers in Vietnam who have engaged in smoking cessation services and successfully write quit messages for other smokers! Further, we will send smokers novel two-way text messages assessing their interest in using quitline services.

Goal 2: Encouraging smokers to accept counseling services

Quitlines have been demonstrated to be an effective intervention.[7] These telephone counseling services can be helpful because trained counselors can help callers select the appropriate cessation services for them (i.e., written information, call back service, quit courses, computer-based assistance, pharmacotherapies or some combination). These trained counselors have a high level of expertise and can help a wider variety of populations with specific needs. Call-back strategies were also shown to be helpful, which included an increase in adherence to nicotine replacement therapy, and to help with relapse prevention.

In the U.S., quitlines have combined provision of nicotine replacement therapy with telephone counseling. An Ohio tobacco quitline was designed to provide each participant up to five proactive telephone calls after initial contact with the quitline. After 2005, this quitline provided a free 4-week supply of NRT to all of its callers who met eligibility criteria. Inclusion criteria were that participants had to be over 18 years of age, not pregnant, and not have any cardiovascular conditions. Overall, the number of calls from September 2004-June 2005 was 2,351 intake calls per month. From July 2005-April 2006, the call volume averaged 3,606 calls per month, which was a statistically significant increase from the pre-NRT sample ($p<.0001$). Six-month abstinence among all quitline callers increased from 10.3% before the availability of NRT to 14.9% after free NRT was provided. The odds of quitting for at least 7 days were significantly higher for the post-NRT sample than the pre-NRT sample (OR=1.28) after controlling for baseline differences between the two groups.[20]

In the U.S., quitlines (and other public health quit smoking resources) have been underutilized. Interventions to increase use have included connecting with clinics (Fax 2 Quit) and email/text motivational reminders.[21] In Vietnam, the quitline has only been called 25 times per day over the past 6 months, but has much more capacity. Recruitment strategies using texting are more novel for smoking, but texting reminders have been used to increase use of services in multiple health domains.[22-24]

M2Q2 Theoretical Constructs

In addition to the general framework of tailoring to a smoker's readiness to quit,[4] our text messages are designed around constructs from Social Cognitive Theory. A core construct from Social Cognitive Theory is self-efficacy.[13] Self-efficacy has been defined as the perceived capacity to perform a behavior.[14, 15] Self-efficacy can influence

outcome expectations, the estimation that a given behavior will lead to a certain outcome. As described in Figure 2, self-efficacy can lead to smokers setting goals (like setting a quit date, engaging in quitline services). The constructs from Social Cognitive Theory have also been used as the basis for training of quitline counselors in the U.S.,[25] and also those of the Bach Mai quitline. As self-efficacy is an important process by which M2Q2 is designed to increase cessation, we will include a measure of self-efficacy as a secondary outcome (in addition to measuring biochemically verified smoking cessation).

Building on Past Experience Working with communities and the Vietnam Ministry of Health

Our joint UMass and Vietnamese team recently completed a pilot feasibility study, Chúng ta nói về bệnh Tăng huyết áp – (We Talk about Our Hypertension). In this study, we randomized 4 community health clinics (and an accompanying 160 patients) to either a didactic or storytelling intervention. The storytelling intervention included stories about strategies for coping with hypertension, with Vietnamese patients speaking in their own words, and didactic content about the importance of healthy lifestyle behaviors including salt reduction and exercise. The storytelling intervention was delivered by two DVDs at 3-month intervals. After obtaining informed consent, a trained community health worker introduced and explained the DVD to the patient and provided instruction in its use. At three months, a study visit was scheduled for a "post-media" interview and re-measurement of blood pressure by a trained community health worker. Most assessments were accomplished in clinic, but some were conducted in the home by community health workers. The mean age was 66 years and 54% were men. Most participants described both interventions as understandable, informative, and motivational. Between baseline and 3 months, mean systolic blood pressure declined by 8.2 mmHg (95% CI: 4.1 - 12.2) in the storytelling group and 5.5 mmHg (95% CI: 1.4 - 9.5) in the didactic group.

Innovation:

The Digital Age has dawned for behavioral interventions for smoking cessation, allowing smokers access to technology-assisted tobacco interventions at the point of need.[26-28] Effectiveness evidence for technology-assisted smoking cessation systems is increasing rapidly.[26, 28, 29] mHealth is a growing industry, yet very little is known about its integration into clinical care or public health,[30, 31] especially in international settings. Text messaging is an opportunity to provide automated, tailored and timely information to patients.[30, 32, 33] It is low cost and instant, and has been found to be not very intrusive to daily living.[34]

We propose to test a novel combination of motivational strategies in this intervention. First, local community clinical services (community health centers) will

refer smokers to our texting system. Next, smokers will receive motivational texts, brief assessments with positive feedback, and reminders to engage with the quitline. Consistent with our prior work, we expect the texting system to have a direct impact on quitting smoking. Finally, smokers who are interested in attempting to quit will engage with the quitline and receive counseling and nicotine replacement therapy, which will also result in increased cessation. Our motivational texting system has several innovative aspects.

- Key to the texting system success will be content that is patient-centered and culturally relevant. Prior research in messaging systems has used expert-written messages. We will recruit Vietnamese smokers to write messages for other Vietnamese smokers, adding their voices to the system.
- Further, most motivational systems are targeted to smokers who are actively trying to quit (including NCI's Smokefreetxt (https://smokefree.gov/smokefreetxt), a system designed for smokers trying to quit within 14 days). Ours is one of the few motivational messaging systems that have demonstrated prior evidence of effectiveness in a population not yet ready to quit.

In our prior trial, the motivational system was effective, independent of use of NRT or quitline use. In this study, we are expanding the goals of the system to include encouraging use of the quitline and NRT. Prior research has suggested that reminder texts can increase use of preventive services.[35]

Investigators have previously worked with clinics to implement smoking cessation counseling, and deliver comprehensive services. Integrating time-intensive counseling and protocols for treatment into clinics, especially busy, under-staffed clinics like those we have worked with in Vietnam can be challenging. Also, note that 27% of smokers have not seen a doctor in clinic in the past year, according to the 2010 Global Adult Tobacco Survey.

Our approach is different; we recognize the challenges of implementation in rural health clinics in Vietnam, as we have worked with the clinics and their outreach through community health workers. We plan to work with clinics, including their community health workers, to help smokers connect to the texting system, but not to deliver a comprehensive intervention themselves. In our prior work with these Vietnamese clinics, we conducted a focus group with the three directors of the community health centers (CHC) in the Vietnamese communes we surveyed. The directors agreed that there is an important unmet need for additional community-based interventions. One CHC director stated that, "Since the CHCs are limited in budget and trained staff, providing a technology-based intervention to this population should result in improved attitudes, knowledge, and behaviors."

6. INCLUSION AND EXCLUSION CRITERIA*

To be enrolled in this trial, consenting adult men and women need to fulfill each of the following criteria: (1) be a resident of the selected commune; (2) be a current smoker; 3) be able to receive texts and read text (literate); (4) not be cognitively impaired (as assessed by study physicians); (5) not be a smoker who helped develop the motivational texts used in the intervention; and (6) not be living in the same household as another participant in the study. As the prevalence of smoking in women is rare, a simple sampling approach might yield few or no women in the sample. In accordance with the NIH criteria for rigor and reproducibility, emphasizing inclusion of both sexes into human research, we will plan a stratified sampling plan to assure that at least 15% of the sample is women smokers. We will plan to recruit smokers regardless of their readiness to quit. Minors, unable to consent adults, pregnant women, or prisoners will not be included. We will be recruiting non-English speaking subjects, particularly individuals who speak Vietnamese. While the age of majority in Vietnam is 16, the legal age for smoking is 18 and thus we will only enroll individuals aged 18 years and older.

Inclusion criteria for the Aim 3 qualitative interview participants is the same as for the trial, with the additional criteria that the participants must have finished the six-month trial and have agreed to study staff contacting them for future studies.

7. STUDY-WIDE NUMBER OF SUBJECTS*

We plan on recruiting 750 Vietnamese smokers in Vietnam. There will not be any recruitment in the United States.

8. STUDY-WIDE RECRUITMENT METHODS*

We will recruit smokers over 48 months. Recruitment will be conducted by both clinic staff and community health workers. We will recruit men and women, and plan for recruiting 15% women. The study will be conducted in the Red River Delta Region, an agriculturally rich and densely populated area in northern Vietnam, with most of the region devoted to the cultivation of rice. In this region, communes in Hung Yen province were selected based on their general representativeness. Hung Yen province has a population of about 1.2 million, organized into 10 districts and 161 communes. All communes in Hung Yen province have adequate electricity. Data from a national survey in 2010 showed that 94% of households in Hung Yen province have a television, and 43% of households have landline phones. Use of text-enabled phones has increased dramatically since 2010. In 2012, a survey found that 84.5% of participants had a mobile phone, and 72.1% of the phones were capable of text messages. Note that although prevalence of text-enabled phones is high, we have budgeted to provide all patients with a phone and cellular service to assure that all eligible smokers can participate.

Four communes (Xuan Quan, Viet Hung, Tan Viet and Bach Sam) located in four different districts in Hung Yen province will be included based on their general representativeness to the rural northern Vietnamese population, and because we have developed infrastructure to support technology-assisted behavioral interventions through community health centers (CHCs) in these communes. Each of the selected communes satisfy the following criteria: (1) have a community health center with a medical doctor; (2) are not currently participating in other studies for smoking cessation; and (3) have a minimum geographic separation of 12 kilometers (7 miles) from all other study communes to minimize possible contamination.

We will plan to recruit smokers regardless of their readiness to quit. Participants will not be compensated, other than being provided a cellphone if they currently do not own one, or prepaid minutes credit with their cellphone carrier if they already own a cellphone. A subset of participants who completed the six-month study activities will be invited, using the main trial's recruitment methods, to complete a qualitative interview (N =30). These participants will include both former intervention and comparison participants. Participants will be provided an incentive of $15 to participate in the semi-structured individual interviews. All United States Dollar amounts are approximate due to the conversion rate to Vietnamese dong.

For additional details on recruitment procedures, refer to #11 Procedures Involved.

9. STUDY TIMELINES*

The duration of an individual subject's participation in the study is 6 months (baseline survey, texting system, quitline data, and the 6-month follow-up survey). For those asked to complete the qualitative interview, this will take no longer than one hour after they have completed the six-month follow-up survey. The duration anticipated to enroll all study subjects is 2 years, 2 months. The estimated date for the investigators to complete this study with primary analyses is: the middle of year 5 (55 months).

10. STUDY ENDPOINTS*

The main dependent variable is patient tobacco cessation rate (quit rate) at six months. The primary independent variable is assignment to intervention or comparison group. We have designed a patient-level analysis around point prevalence cessation. 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. Our secondary outcome measure is self-efficacy. We hypothesize that the self-efficacy (SEQ-12) scores will be higher in intervention than comparison. The SEQ-12 is a 12-item questionnaire with 6 questions under two domains, internal and external stimuli. 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 more from baseline to six months for the intervention group than the control group. We will compute the scores at baseline six months in the two groups.

11. PROCEDURES INVOLVED*

Patient recruitment will be conducted by clinical services staff (staff in clinic and their affiliated community health workers). At the beginning of the study, all study personnel and community and quitline collaborators will be trained carefully about study protocol and standard operational procedures (SOP). Treatment fidelity will be determined by the Vietnam Co-PIs directly monitoring 20% of all study enrollment and follow-up visits and completing a fidelity checklist. As noted, as 27% of Vietnamese male and female smokers have not been to a clinic in the past year, we will recruit both through clinic staff and through outreach community health workers. Sampling frames (household/resident lists) that comprise all adult community members will be obtained from commune records. Based on the sampling frame, adult commune residents will be randomly selected for screening for smoking status. To minimize selection bias, enrollment of patients will proceed in a systematic and sequential manner until the full sample size has been attained. Patients who agree to participate will complete informed consent procedures, baseline survey, and will be provided a text-enabled phone as needed.

Randomization: Participants will be blinded to randomization. All smokers will be told that they will be randomized to one of two different ways to support thinking about quitting smoking. In addition to our primary points of innovation, we will use an innovative mHealth randomization strategy. Allocation of participants to study arms will be based on a permuted block scheme in which treatment assignments are made within blocks so that numbers assigned to each treatment arm are equal after a block has been filled. Blocks of various sizes (2, 4, 6) will be used in random order to facilitate allocation concealment. Similar to our prior technology-based trials, we will embed randomization within the technology. At enrollment, study staff will conduct a baseline survey with participants. At the end of the baseline assessment survey, study staff will enter the participant ID and participant mobile phone number from the survey into our texting system, and the system will look up the next allocation within the table, and adapt based on the allocation assignment. Using this technique, both smokers and the study staff will be blinded to allocation during the initial session. In our prior technology-assisted randomized trials, we have embedded randomization within the technology.

Baseline data collection (see M2Q2_Baseline_Survey): will include patient demographics, comorbidities, cessation treatment beliefs scale, and self-efficacy. Self-efficacy will be measured with the SEQ-12.[36] The SEQ-12 is a 12-item questionnaire with 6 questions pertaining to internal stimuli and external stimuli domains each. Two composite scores are computed for each of these domains by adding the individual items. Self-efficacy will be assessed at baseline and follow-up.

Measures through texting: as described above, we will have data collected through texting, including measure of readiness to quit, abstinence assessments, and interest in use of the quitline.

Quitline referral tracking – quitline staff will record details of intake assessment (time on call, readiness to quit, quit date and goal-setting) and fidelity of follow-up call completion. They will also document distribution of NRT lozenge and smoker use of NRT during follow-up.

Follow-up: All participants will be followed-up with 6 months post-enrollment. To minimize losses to follow up and missing data, one week before the scheduled follow-up visit study staff will contact participants by either phone to remind them about their subsequent clinic visits. For participants who miss the follow up visits at the clinic, trained study staff will conduct the interview via telephone. Biochemical verification of smoking cessation will not be obtained for participants completing the follow-up interview via telephone.

6-month data collection (see M2Q2_6moSurvey): A paper survey will be used to collect repeat data on key baseline measures (SEQ-12), and measure smoker perceptions of the intervention supporting smoking cessation. Study staff will determine current smoking through self-report (7 day point prevalence cessation) based on the following question “Do you currently smoke cigarettes (smoked even 1 puff in the last 7 days)?” and then verify with a carbon monoxide breath monitor.[37] Patients who respond “no” to smoking now will be classified as non-smokers if their carbon monoxide measurement is less than 10ppm. For participants conducting the interview via phone, staff will collect and enter data via REDCap.

Qualitative Interview (see document titled “M2Q2_QI_Guide”): We will conduct a detailed qualitative interview with up to 30 participants to identify potential facilitators and barriers to study participation. Interviews will be conducted in-person at community health centers of participating study sites or by phone. We will audio-record interviews; the audio-recorded interviews will be transcribed and entered into NVivo 10 qualitative analysis software. We anticipate that each interview will take up to one hour. We will review these results as a group to make appropriate protocol changes. Participants will

be provided an incentive of $15 to participate in the semi-structured individual interviews. All United States Dollar amounts are approximate due to the conversion rate to Vietnamese dong.

12. DATA AND SPECIMEN BANKING*

N/A

13. DATA ANALYSIS AND MANAGEMENT*

Power calculations are based on having complete data on a sample of 600 for the intent-to-treat analysis. Note that for our analysis with missing = smoking, we will use the full sample randomized. As discussed above, all participants randomized to the intervention will receive the motivational messages. However, participants will choose whether or not to use the quitline and NRT.

Our calculations are based on several assumptions. First, in the U.S., rates of cessation without intervention have been documented to be 7-10% per year.[38] In Vietnam the rate of smoking is high, and the annual rate of cessation is low. To be conservative, we have estimated the control cessation rate to be 10%. Based on our prior trials, we have detected a 9% difference in intervention and control, comparing the motivational messaging system with a robust, website-only control (as we have a simple attention control in this study, the difference may be greater). If we anticipate that 30% of the intervention will engage in quitline counseling and NRT, and that group will have a greater cessation rate (between 20 to 25%), then the overall cessation rate averaged across the intervention group will be greater than 10%. Based on these assumption, we have assessed power for a range of assumptions (with difference in cessation from 7% to 10%). We are powered to detect a 10% difference (alpha at 0.05) with 91% power.

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. 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.[39, 40]

Main outcome: six-month point prevalence cessation: The main dependent variable is patient tobacco cessation rate (quit rate). The primary independent variable is assignment to intervention or control group. We have designed a patient-level

analysis around point prevalence cessation. 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.

Because we are interested in the effect of the intervention in the sample targeted, we will conduct an intent-to-treat analysis with all those randomized analyzed from MHV use at follow-up. As many in the encouragement arm will not participate, this ITT does not directly assess the intervention-attributable effect. Thus, in addition to ITT, we will utilize a complier average causal effect (CACE) analysis to estimate intervention effects for those who engaged with the intervention.[41] CACE estimation makes it possible to estimate the intervention effect for only those who engage. The CACE estimation considers both random assignment and receipt of treatment to estimate intervention efficacy. CACE estimations have been published using instrumental variables, expectation-maximization algorithm, maximum-likelihood, and integrated methods.[42] CACE seeks to compare outcomes for individuals in the intervention condition with those who would have complied with treatment given the opportunity to do so, and can often be used to improve power over ITT methods. Below, we provide power for ITT analyses, and anticipate additional power when implementing the CACE.

Dealing with missing outcomes data: 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 750, our power calculations for outcomes are based on 600 completing follow-up. We will monitor recruitment and retention, and inflate our sample as needed to achieve the resulting sample of 600 completing 6-months. We will estimate potential bias due to drop-outs 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. A challenge for all cessation induction trials is missing outcome data.[43-45] This is especially true in light-touch technology-assisted interventions. Most often, a complete case or missing case (penalized imputation) indicative of smoking analysis has been implemented in logistic regression. However, the reason that we did not use penalized imputation as the primary outcome is that new literature has been published suggesting that penalized imputation (or missing=smoking) is not a conservative approach, and can be biased toward the intervention.[44] Thus, for studies with missing cessation data greater than 10-20%, experts recommend using selection models to examine the robustness of findings.[43] We will compare characteristics of patients who remained in the trial and those lost to follow-up. Using a generalized linear model with a logit link to evaluate cessation outcomes and GEE methods to account for clustering within practices, we will

implement a selection model using inverse probability weighting to determine the potential effect of missing data. First, based on covariates available within the dataset, we will develop a logistic regression model to predict the amount of missing data. Then, we'll calculate the inverse probability of not being missing and weight the main analysis by this probability.[46]

Secondary Outcome: Self-efficacy: We hypothesize that the self-efficacy (SEQ-12) scores will be higher in intervention than comparison. The SEQ-12 is a 12-item questionnaire with 6 questions under two domains, internal and external stimuli. 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 six months for the intervention group than the control group. We will compute the scores at baseline six months in the two groups. We will evaluate whether the intervention differences change over time (i.e., is there an intervention and time interaction?). To address this question, we will use a random-effects model of the form:

$y_{ijt} = \alpha + \gamma_i + \beta_j + \delta_t + (\beta\delta)_{it} + u_{ij} + e_{ijt}$

where, y_{ijt} is response at time t for the j-th subject in the i-th group, α is the intercept, γ_j is the vector of effects associated with covariates, β_i is the main effect for the intervention group, δ_t is the main effect for time, $(\beta\delta)_{it}$ is the effect for the interaction between intervention group and time, u_{ij} is the random effect corresponding to the j-th subject in the i-th group (assumed to be $N(0,\sigma_u^2)$), and e_{ijt} is the term accounting for sampling variability (assumed to be $N(0,\sigma_e^2)$). The coefficient $(\bar{a}\ddot{a})_{it}$ 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.

Portable devices used to collect data (audio recordings from qualitative interviews) will be PHAD-issued devices and files will not be encrypted during the recording, but the recordings will be transferred as soon as possible (i.e.: typically within the same day) to REDCap. Once the files are transferred, they will be deleted from the portable devices. Data gathered through qualitative interviews will be managed and coded using NVivo 10. An integrated approach to coding will be used, employing a coding start-list based on protocol questions (deductive coding) and open coding driven by emersion in the qualitative data (inductive coding). Duplicate coding will be conducted with at least 10% of the interview transcripts and coding comparisons will be run to ensure inter-rater reliability. Disputes in coding decisions will be discussed within the research group until resolved. We will continue to test and refine coding until we attain a Kappa >.80. NVivo qualitative analysis software will be employed to generate coding reports that summarize participant responses, ideas, and reflections related to

relevant research questions. Two members of the research team will complete the thematic analysis.

14. PROVISIONS TO MONITOR THE DATA TO ENSURE THE SAFETY OF SUBJECTS*

Consistent with NIH policy, the purpose of the Data and Safety Monitoring Plan (DSMP) is to specify the procedures and rationales of the current study to ensure the safety of participants and the validity and integrity of the data. This plan specifies who will examine the data and any adverse events, how often, and what they are authorized to do. Since this trial takes place in Vietnam and is a Phase III study including NRT and our behavioral intervention, we will establish a Data and Safety Monitory Board (DSMB) at the Institute of Population, Health, and Development (PHAD) in Vietnam and a Data Oversight Committee (DOC) at the University of Massachusetts Medical School.

The DSMB is charged with reviewing protocols and consent documents for this trial, monitoring safety issues throughout the study and the quality of the accumulating data, providing guidance on interim analyses and stopping rules. They will also serve as a liaison among the study investigators, the PHAD IRB, the UMMS DOC, the UMMS Office of Human Research Protections (IRB), and the National Institute of Health (NIH).

DSMB Membership

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.

DSMB Responsibilities and Actions

The DSMB will have the following responsibilities:

1.) Review and approve, disapprove, or suggest modifications to the randomized trial protocol and/or consent documents to assure both scientific integrity and that the study adheres to human subject protection policies.

2.) Monitor, provide feedback, and report on scientific and ethical issues related to study implementation for the protection of human subjects and advise on ethical issues related to adverse events. The DSMB will monitor adverse event reports for purposes of determining whether their nature, frequency and severity are consistent with expectations. The DSMB, in coordination with the PI, Dr. Sadasivam, reports to the IRB and NIH any unanticipated problems involving risks to subjects. Along with the IRB and NIH staff, the DSMB can recommend remedies or other appropriate actions such as introducing new monitoring protocols, altering inclusion or exclusion criteria, or recommend changes in the informed consent documents.

3.) Ensure that the study protocol maintains patients' confidentiality in a manner that is appropriately balanced against issues of clinical care and safety.
4.) Monitor data regarding the efficacy of the study. The DSMB will review data for outcome events by treatment group. The DSMB will decide whether the trial should continue with or without further enrollment of new participants. The DSMB has the authority to halt the trial as needed.
5.) To monitor data management activities. The DSMB may ask to review data relevant to quality control. The DSMB will review requests for interim analyses and approve, disapprove, require additional information, or defer decisions.

DSMB Meeting Schedule

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 DSMB meetings will be conducted via teleconference. The Board and the PI will decide upon the format of the meetings. Additional telephone conferences will be held if doing so is recommended by the DSMB.

DSMB Reports

The PI, Dr. Sadasivam, and study team will submit statistical reports to the DSMB one week prior to the scheduled meeting. These reports will include all reported data up to and including 14 days prior to the reporting deadline (except for Serious Adverse Events, which are to be reported within 24 hours of the event). For each meeting at which the study is to be considered or monitored, the investigators will present an overall progress statement. This brief statement should contain the assurance that the investigators have considered the clinical trial's progress and that there is or is not evidence of safety issues that should be addressed by the DSMB. In addition, the report will contain any changes to the study protocol, recruitment, retention, and tracking of study patients (using a CONSORT diagram), a summary of all adverse events and severe adverse events, baseline measures and demographics of all patients reporting adverse events, and any other information requested by the DSMB.

Data Oversight Committee

The Data Oversight Committee (DOC) will be responsible for ensuring the project is in line with US Regulations and Compliance of human subject research. The DOC will be comprised of individuals with no direct involvement in the study or conflict of interest with the research team conducting the randomized trial. The DOC will include individuals with expertise in: 1. Clinical research in Tobacco; 2. Health Informatics and/or Information Technology intervention research; and 3. Biostatistical experience.

The DOC will be responsible for reviewing all minutes, reports, and recommendations of the DSMB meetings and providing appropriate feedback to the PI, Dr. Sadasivam. The DOC will convene within 2 weeks following each DSMB meeting with DOC meeting materials, including DSMB meeting minutes, being circulated at least 1 week prior to meeting. The DOC meeting will be conducted via teleconference.

Adverse Events

Dr. Sadasivam will provide monitoring for all adverse events. All adverse events/effects will be recorded in the research record and any reports of adverse events will be reviewed by the PI or his designee, who are available 24 hours/day. All non-serious adverse events will be reviewed in a weekly study meeting. Adverse event documentation will include description of the event, ratings of severity and relationship to study medication/study procedures, and follow-up (if any) and outcome. All adverse events, both serious and non-serious, will be summarized in the required report to the IRB Committee(s) for annual study review and renewal. The PI will then comment on the implications to future participants and the need for changes to the risk: benefit ratio for participating in the trial.

Serious Adverse Events

The PI will report to the IRBs, if mandated to do so, all serious adverse events that occur in the context of this randomized trial. In general, a serious adverse event is a defined as a harmful and undesired effect resulting from a medication or other intervention. The event is also: life threatening/results in death OR disabling/incapacitating OR requires or prolongs hospitalization OR was otherwise unanticipated, related to the study procedures or could lead to one of the other serious event conditions

According to UMMS IRB policy, all adverse events and serious adverse events that occur in the proposed study must be reported to the institution's IRB, regardless of whether they are study related or not.

IRB Approval

All study protocols, including the Data Safety and Monitoring Plan, will be submitted and approved by the UMMS and PHAD IRBs.

15. WITHDRAWAL OF SUBJECTS WITHOUT THEIR CONSENT*

N/A

16. RISKS TO SUBJECTS*

The foreseeable risks for participating in this study are small. Having to talk with a quitline counselor about smoking can be inconvenient. Using Nicotine replacement therapy can create negative effects for pregnant women, but they are excluded from this study. We will ensure participants are verbally informed of the details of the qualitative interviews and other study activities as they are delivered, including informing the participant that they do not have to answer any interview questions that they are not comfortable answering, and that they can stop the interviews at any time.

17. POTENTIAL DIRECT 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. We anticipate that participation may increase self-efficacy and subsequent cessation. There is a known gap in the number of participants actively using quitlines in Vietnam for smoking cessation efforts. This study will be one of the first randomized encouragement designs intended to increase usage of available, yet underutilized, resources. This study will also be one of the first interventions to evaluate the potential of innovative mobile health technology to increase self-efficacy and develop new cessation skills for Vietnamese smokers.

18. VULNERABLE POPULATIONS*

N/A

19. MULTI-SITE RESEARCH*

While participant recruitment and data collection will only occur at the Vietnam site, we will ensure that all investigators have the most current versions of the protocol, consent documents, HIPAA authorization, and all other study documents. Furthermore, the protocols, consent documents, questionnaires, and HIPAA authorizations will all be translated into Vietnamese and distributed to participants. We will ensure that IRB approval will be obtained at the Vietnam Ministry of Health prior to initiation of research activities and ensure that all modifications have been communicated to each site and approved by each respective site's IRB. We will ensure that all local site investigators conduct the study appropriately and will check regularly with weekly meetings. Any non-compliance with the study protocol or applicable requirements will be reported in accordance with local policy. All study sites' IRB's (Vietnam Ministry of Health and UMass Medical School) will be informed of any problems, interim results, and the study closure.

20. COMMUNITY-BASED PARTICIPATORY RESEARCH*

N/A

21. SHARING OF RESEARCH RESULTS WITH SUBJECTS*

We will not be sharing research results with subjects or others. Only study staff will have access to research results once the study has concluded, and this is strictly for analytic purposes.

22. SETTING

Our study will be conducted in the Red River Delta Region, which is an agriculturally rich and densely populated area in northern Vietnam, with most of the region devoted to the cultivation of rice. In this region, communes in Hung Yen province were selected based on their general representativeness. Hung Yen province has a population of about 1.2 million, organized into 10 districts and 161 communes. All communes in Hung Yen province have adequate electricity. Data from a national survey in 2010 showed that 94% of households in Hung Yen province have a television, and 43% of households have landline phones.[47] Use of text-enabled phones has increased dramatically since 2010. In 2012, a survey found that 84.5% of participants had a mobile phone, and 72.1% of the phones were capable of text messages.[48] Note that although prevalence of text-enabled phones is high, we have budgeted to provide all patients with a phone and cellular service to assure that all eligible smokers can participate.

Four communes (Xuan Quan, Viet Hung, Tan Viet and Bach Sam) located in four different districts in Hung Yen province will be included, based on their general representativeness to the rural northern Vietnamese population, and because we have developed infrastructure to support technology-assisted behavioral interventions through community health centers (CHCs) in these communes. Each of the selected communes satisfy the following criteria: (1) have a community health center with a medical doctor; (2) are not currently participating in other studies for smoking cessation; and (3) have a minimum geographic separation of 12 kilometers (7 miles) from all other study communes to minimize possible contamination.

In local clinical services in Vietnam, the health system is organized into four levels, namely central, provincial, district hospital, and the lowest level, which includes the CHCs that are responsible for providing primary health care and outpatient services. Patients who smoke are typically treated and managed at the CHC. Based on national benchmarks, a CHC typically has 5 staff members including a medical doctor, an assistant doctor, an OB-GYN nurse, a midwife, and a nurse. Usually, there is one CHC for a commune. As an extended arm of the CHC, community health workers, regulated by the Ministry of Health,[49] serve as liaisons between the health center and the community. Three quarters of all communes in Hung Yen province meet national benchmarks for CHCs and all have at least one community health care worker.[50]

Because an established infrastructure of community health workers exists throughout Vietnam and in our proposed study communities, we will build upon this important resource for health education in this population. Previous work by Dr. Allison and his team focused on community health worker programs for diabetes in the U.S. revealed several implementation problems including fidelity of intervention delivery and the need for more resources by community health workers.[51] Similar sentiments were echoed by our formative work in Vietnam.

23. RESOURCES AVAILABLE

- The PI will be responsible for all aspects of the project, including planning and conducting the study, analyzing the data, and writing publications.
- The Co-PI will be responsible for providing regular and ongoing input to the design and conduct of this project with the principal study investigators in Vietnam. He will assist in the design of the study's data collection instruments and data collection activities, the intervention, and he will play a primary role in the analysis of all study related data and its write-up and preparation for peer reviewed manuscripts. The Co-PI will work closely with the investigators based in Vietnam to oversee the development of the patient interventions and their implementation and to ensure a smooth and orderly flow of the study and its quality control.
- The Co-PI will be in direct and regular contact with the PI and key investigators in Vietnam for all study related operations, weekly telephone calls, and ongoing email correspondence. The Co-PI will play a primary role in supervising the development and programming of the intervention system.
- The Biostatistician, will direct the creation of randomization tables and data collection systems in year 1, monitoring of data collected in years 2-4, and be the primary person responsible for statistical analyses for evaluating processes and outcomes of the study in year 5. We anticipate increased effort required in Year 5 to conduct analyses and have thus budgeted for increased effort in this year compared to years 1-4.
- The project director, will be responsible for directing the initiation of recruitment for the study. In year 5, the project director will also have additional responsibilities directing the completion of the study, as well as participate in the writing of manuscripts. For these reasons, we have budgeted an additional 10% effort in years 1 and 5, and an additional 5% effort in Year 2 of the project compared to effort budgeted in years 3-4 when recruitment and follow-up protocols should be well established and study activities ongoing.
- The programmer will be responsible for preparing the systems for this project in year 1, including integrating the randomization design, preparing the text messaging for the targeted smokers, and developing any administrative pages for monitoring the recruitment and data collection. In years 2-5, she will be responsible for maintenance, adjustments, and any trouble shooting of the systems, conduct weekly check of text message logs for messages sent to study participants to allow for timely detection of any glitches.
- The Research coordinator will design, prepare and assemble all materials for the study. She will prepare all IRB and human use protocol materials, ensuring annual renewal of IRB. We are anticipating an increased effort required for initial IRB submission and protocol development in Year 1 as well as completing the study and

producing final datasets and reports in year 5. We have thus budgeted for additional efforts in these years compared to effort budgeted in years 2-4.

24. LOCAL RECRUITMENT METHODS
N/A

25. LOCAL NUMBER OF SUBJECTS
N/A

26. CONFIDENTIALITY
Source of Materials

The data that will be collected for this study include rankings of existing messages translated into Vietnamese and new messages written by Vietnamese smokers (Aim 1). In Aim 3, participants in the randomized trial (both intervention and control groups) will undergo standardized survey administration and carbon monoxide verification at baseline and follow-up, as well as answer assessment text messages intermittently throughout the course of the study. See grant narrative section D.5 for more information about the assessments. All data will be obtained by trained study staff supported by the project and entered directly into electronic forms on a secure website designed for this purpose.

We will use services we have currently developed for our texting system. The texting service will be responsible for sending the texts, as well as receiving the text responses (ratings and time to first quit). The software program we have developed will use a secure Application Programmable Interface to the service to forward the patient's phone number and send and receive the texts. To minimize risks, the motivational messages will not contain any personal health information. The software program will then read the texting service servers to extract the data and enter into our regulated environment. As soon as this is complete, the program will then delete the data from the texting servers. Please note that the texting service does not store the phone numbers, it will only use them to send and receive messages. The phone numbers will only remain on Vietnamese servers for a brief period. Phone number data will not be transferred to any site outside of Vietnam. Participants will be informed of the potential risk to confidentiality of sending and receiving text messages during the informed consent process.

Protection of Data

Participants will be identified with a study number and the key will be located centrally and securely; and be accessible only to certified study personnel on an as needed basis. All patient contact, including consent, interviews, and all study procedures with human subjects will occur onsite in Vietnam. All data will be collected by PHAD investigators and staff under sub-award from UMMS. All data will be de-

identified according to HIPAA standards prior to transfer to UMMS investigators and staff for analytical purposes. The UMMS Principal Investigator, statistician, project director, and research coordinator will have access to identifiable data when in Vietnam. The Investigator and project coordinator in Vietnam will also have access to identifiable data.

Study staff will not be allowed to create or keep any other data records. In addition to demographic, treatment, and outcomes data; limited personal identifiers about each patient will be obtained. These will include patient name, address, telephone numbers, and date of birth/age. These will be abstracted onto a separate confidential form in the data system, with special security access, and will not be transferred outside of Vietnam. Personal identifier data will be linked to the “de-identified” electronic case report form by a study code number – this link will only be available to the study PI and Vietnamese study staff. This linkage will allow for the long- term follow-up of smokers but will also allow us to keep the identity of study subjects secure. In addition, this linkage will allow us to cross-reference data to several sources (e.g., local death certificates) to determine whether a subject has died during the course of follow-up.

Portable devices used to collect data (audio recordings for qualitative interviews) will be PHAD-issued devices and files will not be encrypted during the recording, but the recordings will be transferred as soon as possible (i.e.: typically within the same day) to REDCap. Once the files are transferred, they will be deleted from the portable devices. Data gathered through qualitative interviews will be managed and coded using NVivo 10.

All records consisting of personal identifiers will be destroyed upon completion of the study by shredding of the hard paper copy and destruction of the electronic files. Medical record research material will be limited to that available in the inpatient and outpatient medical records. All procedures will be HIPAA compliant. IRB approval will be sought at each study site before study initiation.

Potential Risks

The risks of the study are not high, and thus the safety monitoring plan has been matched to the risk to subjects in this study. 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 who call the quitline may receive over the counter Nicotine Replacement Therapy. 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.

The lozenges will be provided in 4mg doses. Risk of nicotine replacement therapy has been evaluated in detail. As this treatment has less nicotine than cigarettes, it is in general a risk reduction from active smoking. All participants who have a Food and Drug Administration contraindication to nicotine lozenge will be excluded.

Patients may become uncomfortable when asked about psychosocial factors such as smoking cravings or urges. Patients will be reminded repeatedly that they are under no obligation to respond to any question, and interviewers will be trained, certified, and supervised in appropriate interview techniques. Also, interviewers will be trained to recognize responses suggestive of imminent risk (e.g., patient suicidal ideation) and how to immediately contact medical personnel for help.

There are no other anticipated risks associated with the design of this randomized trial. We will work closely with the Committee for the Protection of Human Subjects at the UMMS as well as various IRB committees, and data abstractors during the design and conduct of the proposed study to ensure the protection of patient confidentiality and compliance with HIPAA regulations.

Protection against risk:

This study has been designed with strict safeguards against the disclosure of patient confidentiality, the major potential risk. Other risks are very unlikely (e.g. patient agitation) but safeguards against them will be in place. Accordingly, we believe that the risks to subjects are reasonable given the importance of the knowledge to be gained. We have minimized data collection to that which is needed to answer study hypotheses. We have stringent protection against breach of confidentiality using secured servers and locked office spaces for data entry at UMMS. The study statistician (Dr. Person) will do periodic checks to ensure that participant confidentiality is protected at all stages of data management and analysis. At the start of the study all project team members will be trained in practices that ensure participants' confidentiality and privacy.

27. PROVISIONS TO PROTECT THE PRIVACY INTERESTS OF SUBJECTS

We will make patients feel at ease by recruiting through clinical services staff (staff in clinic and their affiliated community health workers). This will be done in a private setting. At the beginning of the study, all study personnel and community and quitline collaborators will be trained carefully about study protocol and standard operational procedures (SOP). Treatment fidelity will be determined by the Vietnam Co-PIs directly monitoring 20% of all study enrollment and follow-up visits and completing a fidelity checklist.

28. COMPENSATION FOR RESEARCH-RELATED INJURY

N/A

29. ECONOMIC BURDEN TO SUBJECTS

The only economic burden that may occur would be that participants may have to travel to their clinical service center. Participants will be provided with a cellphone, if they do not currently own one. Since NRT will be provided, there will be no cost to the subject.

30. CONSENT PROCESS

All study staff will be briefed on the informed consent and will follow HRP-802 INVESTIGATOR GUIDANCE: Informed consent regulations. The consent process for main RCT participants will take place at the participants' community health center. Participants will be afforded the opportunity to thoroughly read through the informed consent and agree to participate, prior to enrollment. Study staff in Vietnam and quitline counselors will follow-up with participants to ensure ongoing consent. Since we will be obtaining an informed consent from non-English speaking subjects, we will be using a translated consent form. It will be translated into Vietnamese. Vietnamese trained study staff will provide the written and oral consent form in the language that they best understand.

Qualitative interview participants will provide verbal consent for the interview and will be provided with a fact sheet describing this study activity. We are requesting a waiver of consent documentation; please see section 31 below for more details.

31. PROCESS TO DOCUMENT CONSENT IN WRITING

All main RCT participants will provide written informed consent in Vietnamese for study inclusion, administration of surveys, and carbon monoxide verification. Patients will be approached by workers from their local community health center as described in the body of this application. If patients are interested in learning more about the study, study staff will then provide a brief overview of the study including the reason the study is being performed, a description of the study design, and the patient's role in the investigation if he or she decides to participate. The patient will be informed of the potential benefits of the study. The patient will also be informed that the design of the study requires collection of personal identifiers (as described previously), of the safeguards in place to protect that information, and of his or her right to withdraw from the study at any time (at which point all personal identifier data collected will be destroyed). At any time, persons may withdraw consent. If patients agree to participate in the study, trained study staff will provide a written consent form in Vietnamese with the UMMS watermark for patients to sign.

We are requesting a waiver of written documentation of consent for qualitative interview participants. We feel that the waiver of documentation of written consent is reasonable in this instance, as:

1. The research presents no more than minimal risk to subjects because it consists of one semi-structured, qualitative interview. This activity is non-invasive and this is a low-risk study.
2. The research involves no procedures for which written consent is normally required outside of the research context. The audio recorded semi-structured interview has appropriate confidentiality protections.

32. DRUGS OR DEVICES

N/A

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