RESEARCH PROTOCOL

(Last updated: December 15, 2021)

Title of Project: Mobile Health Technology for Personalized Tobacco Cessation Support among Cancer Survivors in Laos

Short title: SurvLaos

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Abstract

In Lao People's Democratic Republic (Lao PDR), tobacco smoking prevalence among cancer patients is high: 60% in men and 15% in women. Evidence from developed countries suggests that smoking cessation offers considerable benefits for cancer survivors, including improving cancer treatment outcomes, reducing recurrence rates, reducing second primary tumor development, and reducing overall cancer mortality rates. Despite, ***no tobacco treatment programs are available*** in major (public) hospitals in Lao PDR, including in cancer hospitals/institutions. The parent project (1R21CA253600-01, **OUHSC IRB#: 12189**) aims to adapt and evaluate the efficacy of our theoretically and empirically based mobile health (mHealth) technology to help Lao general patients quit smoking cigarettes. This mHealth automated treatment (AT) approach includes a fully automated, interactive, personalized, smartphone-based intervention for behavioral treatment, delivered through our Insight platform. In year 1 of the parent project, we have been adapting our intervention content to the sociocultural context, language, and communication styles of Laotians. The ***purpose*** of this supplementary project is to expand our mHealth-based AT to ***address the pressing need for smoking cessation among cancer survivors and their caregivers in Lao PDR***. In this project, we will adapt our intervention and materials to make them comprehensible and relevant to these target populations. Next, we will conduct a pilot randomized controlled trial (RCT, N=80) to evaluate the preliminary efficacy of the intervention. Cancer survivors (n=40) and caregivers (n=40) of both sexes who smoke will be recruited at Setthathirath Hospital and Lao National Cancer Center. Similar to the parent project's design, participants will be randomized to 1 of 2 treatment groups: standard care (SC) or AT (20 cancer survivors and 20 caregivers in each group). SC consists of brief advice to quit smoking, self-help written materials, and a 2-week supply of NRT (transdermal patches). AT consists of all SC components plus our fully-automated interactive smartphone-based treatment program, personalized and tailored to cancer survivors or caregivers. The ***primary RCT outcome*** is biochemically confirmed self-reported 7-day point prevalence abstinence at 3 months post-study enrollment. The ***specific aims*** are: 1) to evaluate the feasibility of AT in cancer survivors

and caregivers, and 2) to evaluate the preliminary efficacy of AT in each cancer survivor/caregiver subgroup.

Protection of Human Subjects:

The study protocol and all related research materials (e.g., informed consent forms and assessments) will be reviewed and approved by the Institutional Review Boards (IRBs) of the Ministry of Health - Lao National Ethics Committee for Health Research (NECHR) IRB #1 (IRB00006227) and of The University of Oklahoma Health Sciences Center (OUHSC). Our collaborative hospitals—Setthathirath Hospital and Lao National Cancer Center—are under supervision/management of the Ministry of Health of Lao PDR and have assurances relying upon the NECHR IRB#.

A. SPECIFIC AIMS

The specific aims are to:

- **Aim 1:** Evaluate the feasibility of AT in cancer survivors and caregivers. *Hypothesis (H1)*: ≥75% of AT content will be viewed/opened as indicated by digital date/time stamp in Insight.
- **Aim 2:** Evaluate the preliminary efficacy of AT in each cancer survivor/caregiver subgroup. *Hypothesis (H2)*: At the 12-week follow-up, 7-day point prevalence abstinence will be higher in the AT (vs. SC) group.
- Aim 3 (capacity building): Advance mHealth research capacity in Lao PDR and sustain the US-Lao PDR research network by supporting Lao investigators through in-person workshops, in-service trainings, online trainings, manuscript preparation, and future mHealth research collaboration and grant applications.

B1. BACKGROUND AND SIGNIFICANCE

Globally, tobacco causes approximately 6 million deaths each year, of which 80% occur in low- and middle-income countries (LMICs).[1,2] Tobacco use is the most important modifiable risk factor for cancer prevention and is a leading preventable cause of death[1]; smoking prevention and cessation are the most impactful and cost-effective interventions among the many recommended evidence-based preventive health services.[3] Despite the need, cessation treatments in LMICs are often unavailable or unaffordable for most people.[1]

Of 7 million citizens in Lao PDR, 51% of men and 7% of women smoke tobacco.[4,5] Although several tobacco control efforts have been implemented in Lao PDR (e.g., taxing tobacco products, expanding smoke-free environments, requiring health warnings on cigarette packaging, and comprehensive bans of tobacco advertising), ***no national tobacco treatment programs are available;***[4,6] we confirmed this in recent discussions with leaders of the National Tobacco Control Committee (NTCC) of Lao PDR. NTCC also described a pilot quitline with telephone counseling at the national Mahosot Hospital. However, funding limitations restrict NTCC's ability to train more counselors and retain them for a nationwide implementation. Thus, ***there is a pressing need for evidence-based and highly scalable tobacco cessation treatment in Lao PDR to prevent smoking-related morbidity and mortality***. Our project will address this unmet need.

Potential of mHealth interventions. The World Health Organization (WHO) acknowledges that mHealth could transform the face of health service delivery across the globe, including in least-developed countries (LDCs).[7] Data from the International Telecommunication Union, which

is the United Nation's official source for global information technology statistics, show that mobile-cellular subscriptions now make up >98% of voice subscriptions in LDCs.[8] Active mobile-broadband subscriptions grew extremely rapidly from 4% in 2007 to 56% in 2017, without signs of faltering.[8] Mobile-phone prices in LDCs, including Lao PDR, decreased from 29% of gross national income per capita in 2010 to 14% by the end of 2014, resulting in increased ownership rates.[9] Worldwide, the Asia and Pacific regions have the lowest average prices of mobile phones and cellular service and the most aggressive competition in prepaid mobile-cellular service.[9] In some LDCs in the region, including Lao PDR, prepaid handset-based mobile-broadband prices are less than 5% of gross national income per capita, making them outstanding examples for affordable mobile-broadband services in LDCs. In Lao PDR, there are 4 major mobile operators, 2 of which launched LTE in 2015.[10] In recent years, mobile-cellular subscription rates in Lao PDR ranged from 56%–68%;[9-11] half of these included mobile-broadband subscriptions.[8] Although these subscription rates are moderate compared with the regional average, the most recent data indicate that Lao PDR was in the top 5 countries globally for increased mobile-broadband subscriptions from 2016–2017,[8] suggesting ***substantial growth in mobile-broadband coverage and usage in the near future***. Most smartphones (80%) in Lao PDR are Android-based (predominantly Samsung and Huawei)[12] and can function in Lao script. In summary, ***smartphone ownership is clearly increasing in Lao PDR, providing an ideal yet largely untapped mechanism to deliver smoking cessation treatment***.

A small but growing body of research indicates that ***mHealth interventions are feasible in Lao PDR***. For example, the Lao PDR Ministry of Health (MOH) supported the use of the Safe Delivery mobile app to provide midwives with direct and instant access to evidence-based and up-to-date clinical guidelines on basic emergency obstetric and neonatal care, making childbirth safer, especially in the most remote areas.[13] Short message service (SMS) is also used in a real-time reporting system for vaccine administration and monitoring.[14,15] The MOH's receptiveness and support of mHealth solutions ***increase the potential for sustainability and widespread adoption of our proposed mHealth intervention approach.***

The effectiveness of smoking cessation interventions using text messaging, traditionally delivered via SMS, is shown in both randomized controlled trials (RCT) and a recent Cochrane review.[16,17] A thorough economic analysis demonstrated that a mobile phone text messaging intervention for smoking cessation is cost-effective.[18] Indeed, mobile phone-delivered text messaging has been identified as one of the most affordable interventions[19] and has been endorsed and used by several international organizations, including the WHO, in their global tobacco control efforts.[20,21] Development and evaluation of advanced smartphone-delivered interventions are ongoing. Leading app stores house >170 English-language apps designed to facilitate smoking cessation; however, only 6 of these are scientifically grounded, and only 3 of these have demonstrated a positive impact on abstinence compared to a control condition in pilot RCTs.[22] While the evidence base for these next generation interventions has not yet been established, many agencies such as the US National Cancer Institute have made scientifically-supported apps available for public use.[23]

This supplementary project is ***relevant and responsive*** to the NOSI NOT-CA-21-058 because it focuses on stimulating global cancer survivorship research using mHealth in Lao PDR–a LMIC as defined by the World Bank. Specifically, this study will evaluate the feasibility of a care/intervention delivery model beyond healthcare settings (i.e., mHealth approach) for cancer survivors (6,000 new cancer cases each year, the most common types: liver, breast, lung, and cervical-uterine) and caregivers. The study will adapt an evidence-based survivorship care service (i.e., smartphone-based smoking cessation treatment) in the United States (US) to serve these populations. This application is built on and leverages our existing relationships with stakeholders at national institutions in Lao PDR, including Setthathirath Hospital (SH), Lao

National Cancer Center (LNCC), National Tobacco Control Committee (NTCC), and the Ministry of Health (MOH). Results from this pilot project will be critical for developing our future R01 application and will contribute ***significantly to reducing tobacco-related complications in cancer treatments, co-morbidities, cancer recurrence, and mortality rates in cancer survivors***.

B2. INNOVATION

This is the ***first effort*** to provide a theoretically and empirically based smoking cessation treatment in cancer care in Lao PDR. Our mHealth Technology Shared Resource (Director: Dr. Businelle, co-investigator [co-I]) has developed the novel HIPAA-compliant Insight mHealth platform, which enables ecological momentary assessments (EMA) or just-in-time adaptive intervention (JITAI) for various health behaviors or issues. The use of Insight to manage and deliver AT is innovative in several aspects. Insight allows our AT to ***function autonomously*** and minimizes human involvement, making the approach ***affordable for large-scale implementation in LMICs***. Unlike the traditional short message service (SMS) approach that requires an active cellular network connection, our Insight app will automatically deliver all prescheduled interventions and assessments, ***with or without an active connection***, thus ensuring timely and reliable treatment delivery. Most importantly, Insight enables complex built-in algorithms and branching logic, allowing us to ***create and deliver dynamically and individually tailored treatment content***, using ***near real-time EMA data***. Finally, using the friendly, intuitive Insight platform's interface, Lao researchers can directly manage AT whenever and however they wish ***without knowledge of programming languages***. Thus, in the subsequent implementation phase of AT or in future cancer survivorship research projects, Lao researchers can ***modify the JITAI content to target other behavioral, physical, and psychosocial survivorship outcomes*** (e.g., monitoring cancer treatment compliance, fatigue, and complications; providing timely personalized screening recommendations to detect recurrence early; or improving retention in care).

C1. RESEARCH TEAM

A uniquely qualified multidisciplinary research team has been assembled for this project. Dr. Bui (PI) has extensive experience conducting health promotion research in international settings and in mixed-methods studies.[5,24-30] Other US co-investigators (co-I) bring valuable expertise in mHealth tobacco cessation for low-income and other underserved populations (Dr. D. Vidrine, Dr. Businelle),[31-36] tobacco health risk communication (Dr. J. Vidrine),[37-40] mHealth methodology (Dr. Businelle),[41-44] and biostatistics (Dr. Frank-Pearce).[42,43,45,46] Dr. Xangsayarath is the Director of the National Center for Laboratory and Epidemiology (NCLE), a core unit of the Lao MOH that is responsible for a wide range of public health issues, including tuberculosis and other respiratory infections control. Dr. Xangsayarath was the PI of the National Adult Tobacco Survey (NATS) and has unique expertise regarding tobacco use in Lao PDR. Dr. Phandouangsy is the Deputy Head of the Secretariat of NTCC – an official inter-ministerial governmental authority responsible for tobacco control in Lao PDR, led by MOH. In this position, she provides technical support and oversight to several national tobacco control programs, including all 4 WHO-funded Global Youth Tobacco Surveys since 2003. Dr. Bui has worked with Drs. Xangsayarath and Phandouangsy since June 2017 to analyze the NATS data and prepare manuscripts.[5] Drs. Vangnakhone is the Director of the Setthathirath Hospital. Dr. Arounlangsy is the Director of LNCC.

C2. PRELIMINARY STUDIES

Most relevant to this proposal is our most recent pilot work (with qualitative and quantitative

components) at an HIV clinic in Phnom Penh, Cambodia.[30,47] We linguistically and culturally adapted the intervention for Cambodian smokers, and then conducted a pilot RCT comparing SC (n=25) to AT (n=25) delivered by our Insight™ platform. Of all scheduled notifications and weekly assessments during the 2-month treatment period, 75% were delivered properly (i.e., the phones were properly charged, turned on, and not lost). Of all delivered messages and assessments, 81% were opened, as indicated by the digital date/time stamp. Retention through the end of the 2-month treatment period, as indicated by returning to the clinic for biochemical confirmation of smoking status (expired CO) was very promising – 100% in the AT group and 92% in the SC group. The ***biochemically verified 7-day point prevalence abstinence rate at 2 months was 40% in the AT group and 8% in the SC group*** (RR=5.0; 95% CI: 1.2–20.5). The AT group also scored significantly better (p=0.001) on knowledge items about smoking-related health risks and had a greater, but nonsignificant, change in cessation self-efficacy. Most participants agreed that the AT program was helpful in supporting smoking cessation (92%) and would recommend it to other smokers (88%). These data demonstrate the ***acceptability, feasibility, reliability, simplicity, and preliminary efficacy of our AT technology in LMICs***. This success suggests that ***AT may be appropriate and efficacious in Lao PDR***, a culture comparable to Cambodia.

D. RESEARCH DESIGN AND METHODS

Stage 1: Further adapt the AT intervention

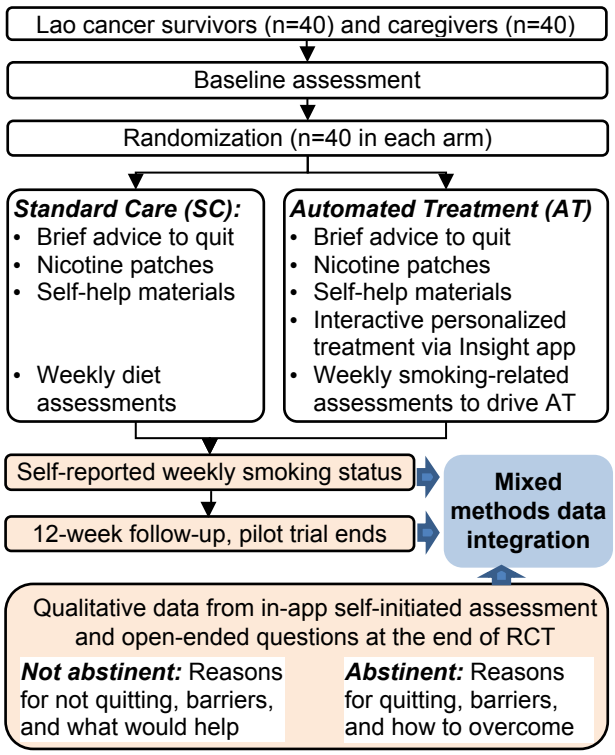
Before conducting the RCT, we will use a multi-step process to adapt our already developed AT intervention for use by the target populations (i.e., cancer survivors and caregivers). These iterative steps include modifying content, user testing and eliciting feedback, and refining. Specifically, we will review all communication messages in the current AT program and modify them to ensure that they are applicable to cancer survivors and caregivers and to both sexes. Then, we will evaluate the AT content applicability, comprehensibility, and linguistic simplicity and clarity with ~10 cancer survivors or caregivers. We will ensure that approximately half of these testing users are women and that the whole testing sample is demographically diverse. Using input and feedback from these testing users, we will revise the AT further if needed. These series of tests and user-feedback sessions to refine the content further and to debug the system will go through an iterative process as needed. AT content taps on theoretical constructs of the Phase-Based Model (PBM)–a theoretical framework specific to smoking cessation used in our JITAI.[48,49]

Stage 2: The pilot RCT

Participant recruitment. We will conduct a pilot RCT (N=80) to evaluate the preliminary efficacy of the intervention (*Figure*). Cancer survivors (n=40) or caregivers (n=40) of both sexes who smoke will be recruited from SH and LNCC in Vientiane (the capital of Lao PDR). At SH, the Department of Oncology and Department of Breast and Gynecologic Cancer serve >200 cancer patients each year. LNCC serves >400 new patients with various types of cancer each year.[50] Research staff will review medical records of cancer patients receiving care at the 2 hospitals in the past 2 years, screen for their smoking status documented in the records, and contact those who smoked for further screening. To recruit caregivers, research staff will contact random cancer patients who ***did not*** smoke and ask if they have a caregiver and if the caregiver smokes. Given the pilot nature of this study, we propose to recruit independent groups of cancer survivors and caregivers who smoke, i.e., no dyads of smokers, to avoid potential interpersonal interactions.

Inclusion criteria. The pilot RCT will include those who are 1) aged ≥18 years; 2) self-reported current combustible cigarette smokers (smoked at least 100 cigarettes in lifetime and currently smoke ≥1 cigarette/day); 3) willing to set a quit date within 2 weeks of study enrollment; 4) able to provide written informed consent to participate; and 5) able to read Lao (score ≥4 points on the Rapid Estimate of Adult Literacy in Medicine—Short Form[51]). *Exclusion criteria* are 1) history of a medical condition that precludes use of NRT; 2) ineligibility to participate based on medical or psychiatric conditions diagnosed by a physician/clinician; and 3) enrollment in another cessation program or current use of other cessation medications. With these criteria in our Cambodian pilot study, we recruited 2–5 participants per day; thus, we expect a similarly high consent rate and feasibility for this study.

Figure: Study schema



Baseline assessment. Enrolled participants will complete a 45-minute baseline self- or assisted interview, managed and delivered by REDCap.[52,53] Participants will be randomly assigned to SC or AT by the REDCap randomization module (simple, 1:1). Smartphones will be loaned to participants as needed. All participants will complete a brief training session on smartphone use and the Insight app. The Insight app also includes a help button for instructions on how to use each feature, which participants can review at any time.

Treatment groups. SC consists of brief advice to quit smoking delivered by research staff, self-help written materials (the WHO's "A guide for tobacco users to quit"[54] that we have translated to and validated in Lao), and a 2-week supply of NRT (transdermal patches). AT consists of all SC components plus a fully automated smartphone-based JITAI that involves proactive, interactive, and personalized messages, images, or videos in Lao. Adapted from the parent study and based on the PBM, AT content is designed to increase motivation, self-efficacy, and use of coping skills and reduce nicotine withdrawal symptoms and stress. AT will begin immediately after enrollment and continue for 12 weeks (about 2 messages/images/videos per day, delivered at participants' preferred time). Quit date is set at day 14 post-enrollment for AT and SC participants. JITAI content for AT participants each week will be ***personalized and tailored*** to each participant's ***baseline information*** (e.g., sex, cancer types, caregiver status, and current health conditions), ***current PBM phase***,[48] and ***responses to the brief weekly EMAs*** that drive AT (see *Measures*). Our AT only targets cigarette smoking because it is the most common type of tobacco used by Lao smokers (95%).[55]

Measures (Table). ***Primary assessments*** will be conducted at ***baseline and at the 12-week follow-up,*** which collect 3 types of data: self-reported data collected by REDCap, expired air carbon monoxide (assessed with Vitalograph BreathCO) to verify smoking status biochemically, and medical record data (for AT personalization). Most of these measures are similar to the parent study and have been translated into Lao. Participants will be compensated US$15 after completing each of the two primary assessments.

Participants in both groups will be asked to complete ***brief weekly assessments*** (EMAs)

via Insight app. AT participants will receive 6 PBM-based smoking-related questions (*Table*) that drive JITAI. To balance the effects of these weekly contacts between the RCT groups, we will ask SC participants to complete a weekly 6-item diet EMA. All participants will be provided a prepaid 3-month unlimited data plan. The ***primary outcome*** is biochemically confirmed (CO level <6 ppm) self-reported 7-day point prevalence abstinence.[56]

Table. Trial Assessments

Variable type	Measure	BL	W*	12
Descriptors/ potential moderators	Demographics; Health Literacy[57]	X		X#
	Alcohol and Drug Use[58,59]	X		X
	COVID-19–related issues,[60] co-morbidities[61,62]	X		X
	Dependence – Heaviness of Smoking Index[63]	X		
Feasibility/ Adherence to AT app	Numbers of messages/images/videos opened and completed; weekly assessments opened and completed; activity logs	Date/time stamps in Insight		
Phase-Based Model mechanisms	Wisconsin Smoking Withdrawal Scale[64]	X		X
	Reasons for Quitting (Intrinsic, Extrinsic)[65]	X		X
	Contemplation Ladder[66,67]	X	X	X
	Kessler Psychological Distress Scale (K10)[68]	X	X#	X
	Positive and Negative Affect Schedule[69]	X	X#	X
	Self-Efficacy (related to smoking cessation)[70]	X	X#	X
Cancer survivorship	Fear of cancer recurrence (survivors only),[71] family support,[72-74] and spiritual well-being[75]	X		X
Qualitative, open-ended assessment	An in-app participant-initiated assessment—"Share with us anything on your mind"—with an open text field to capture the participant's thoughts, feelings, and behaviors	Initiated anytime by participant		
Primary outcome	Smoking status in the past week[76]	X	X#	X
	Expired carbon monoxide at follow-up[56,76]	X	X	X
Secondary outcomes	E.g., number of quit attempts, days abstinent, and other tobacco product use[76]	X		X

Abbreviations: AT, automated treatment; BL, baseline; W, weekly; 12, 12-week follow-up. **Delivered via Insight app; ***Brief versions of the scales.*

Data analysis. Descriptive statistics will be used to assess ***feasibility*** of AT. Regarding ***preliminary efficacy*** of AT, we will use log-binomial regression with an intent-to-treat approach (i.e., missing=smoking) to compare the effect of the treatment on the dichotomous abstinence outcome at 12 weeks post-enrollment, controlling for selected covariates such as sex, education level, and/or baseline stress level. Secondary outcomes will be examined using appropriate linear and generalized linear mixed models with log-binomial and linear regression for binary and continuous variables, respectively. Given the preliminary nature of the RCT, we do not expect to have sufficient power for full hypothesis testing. However, from our previous work, we anticipate that the abstinence at the 12-week follow-up will be 8% in the SC group. With 40 participants in each group, we will have 80% power to detect a difference as small as 20% in smoking abstinence rates between groups (α=0.05, one-tailed, unadjusted).

Mixed methods data analysis.

At the 3-month follow up assessment, we will use additional open-ended questions at the end of the assessment to explore why and how the participants did or did not successfully quit smoking and stay abstinent. Specifically, for participants who were biochemically confirmed abstinent, the questions will focus on what motivated them to quit and how they overcame challenges or barriers to stay abstinent. For participants who were not abstinent, the questions will focus on why they did not or could not quit, what they underwent, what challenges or barriers they had, and what would help them quit in the future.

Two research team members will perform qualitative data coding with the aid of the R-QDA.[77] Discrepancies will be discussed to achieve intercoder agreement. Codes and quotations will be arranged into focused themes (i.e., thematic content analysis) to develop the mixed methods data inventory.[78] Next, we will examine quantitative (RCT) and qualitative data jointly, using the ***integration strategy of explaining*** with the intent to explore why participants could or could not quit and stay abstinent.[78,79] Mixed methods linked data, results, and meta-inferences will be presented in visual joint displays,[79] similar to our previous publication.[80]

Identifiers might be removed and the de-identified information may be used for future

research without additional informed consent from the subject.

E. CHART REVIEW

As described above, at the in-clinic assessments at baseline and at 3-month follow-up, the Lao research team will also collect data from participants' medical records (in addition to interview data and expired air CO assessment). Medical records will be used to collect clinical information, such as comorbidities, recent/current diagnosed health conditions, and current use of medications for AT personalization. In Lao PDR, most of these medical records/data are in paper form; thus, the Lao research staff will review the records/forms and will enter data into the standardized sections/questions in REDCap Mobile app. The tablets that contain the REDCap app are password protected, encrypted, and can be remotely wiped if lost.

F. BIOSPECIMEN

This project does not collect biospecimen.

G. BANKING/REPOSITORY/DATABASE

This project does not bank or store data for future use in other projects.

H. INCLUSION/EXCLUSION CRITERIA

Inclusion criteria. The pilot RCT will include those who are 1) aged ≥18 years; 2) self-reported current combustible cigarette smokers (smoked at least 100 cigarettes in lifetime and currently smoke ≥1 cigarette/day); 3) willing to set a quit date within 2 weeks of study enrollment; 4) able to provide written informed consent to participate; and 5) able to read Lao (score ≥4 points on the Rapid Estimate of Adult Literacy in Medicine—Short Form[51]).

Exclusion criteria are 1) history of a medical condition that precludes use of NRT; 2) ineligibility to participate based on medical or psychiatric conditions diagnosed by a physician/clinician; and 3) enrollment in another cessation program or current use of other cessation medications. With these criteria in our Cambodian pilot study, we recruited 2–5 participants per day; thus, we expect a similarly high consent rate and feasibility for this study.

I. GENDER/MINORITY/PEDIATRIC INCLUSION FOR RESEARCH

I1. Inclusion of Women

We will recruit a pilot sample that mirrors the national smoking prevalence in men and women. Specifically, we will ensure that female smokers are represented in our sample in a manner that aligns with the smoking prevalence by sexes in the real-world. All participants, including men and women, will be encouraged to continue their participation in the study.

I2. Inclusion of Minorities

An attempt to enroll all eligible participants will be made without regard to race/ethnicity. Because this project will take place in Lao PDR, we expect that all participants will be Asian. Among these, approximately 90% will be of Lao ethnicity, 5% will be of other ethnicities (e.g., Chinese, Vietnamese, Thailand), and 5% will be multi-ethnicity. As with all participants, the recruited minority participants will be encouraged to continue their participation in the study.

I3. Inclusion of Children

We have excluded children under the age 18 from the proposed study. In Lao PDR, 18 is the age of majority and, therefore, participants aged ≥ 18 years can consent. We excluded smokers under the age of 18 because the safety of nicotine replacement therapy (NRT) has not been determined for this population. The US Food and Drug Administration has not approved the use of NRT for smoking cessation for children and adolescents.

J. RECRUITMENT AND ENROLLMENT

Cancer survivors (n=40) or caregivers (n=40) of both sexes who smoke will be recruited from SH and LNCC in Vientiane (the capital of Lao PDR). At SH, the Department of Oncology and Department of Breast and Gynecologic Cancer serve >200 cancer patients each year. LNCC serves >400 new patients with various types of cancer each year.[50] Research staff will review medical records of cancer patients receiving care at the 2 hospitals in the past 2 years, screen for their smoking status documented in the records, and contact those who smoked for further screening. To recruit caregivers, research staff will contact random cancer patients who ***did not*** smoke and ask if they have a caregiver and if the caregiver smokes. Given the pilot nature of this study, we propose to recruit independent groups of cancer survivors and caregivers who smoke, i.e., no dyads of smokers, to avoid potential interpersonal interactions.

K. RISKS AND BENEFITS

K1. Potential Risks

The risks to participants are generally minimal and include breach of confidentiality, emotional distress (due to the nature of the assessment questions), and side effects associated with NRT patch use.

There are minimal potential risks to participants from the personal nature of the questions asked regarding health behaviors and health status. Answering the questions may cause participants to feel uncomfortable and/or upset.

Problems associated with the use of nicotine patches include local skin irritation at the site of application, nausea (if the dose of the patch is too high or if high levels of smoking are continued while using the patch), and distressing dreams. Skin allergic reactions have been less commonly reported. Participants may experience unpleasant withdrawal symptoms following smoking cessation. These symptoms include anxiety, restlessness, anger, irritability, sadness, difficulty concentrating, change in appetite, weight gain, insomnia, and decreased heart rate.

K2. Protection against Risks

Protection against Confidentiality Breach: Confidentiality will be maintained for all data and contact information. To protect against the risk of a confidentiality breach, the following steps will be taken:

- REDCap will be used to collect and manage information for most procedures, including screening eligible participants, administering in-clinic assessments at baseline and follow-ups, and capturing participants' information from medical records. REDCap is a secure web-based application designed to comply with all HIPAA regulations. Data will be collected by participants (e.g., self-interviews for baseline assessment) or by research staff (e.g., screening or reviewing medical records) on tablets using the REDCap Mobile App. Each participant will be given a unique identification number (UIN) in this study, and the UIN will be used in all data collection procedures that are managed by REDCap. The REDCap Mobile App employs encryption at-rest on the mobile device's hard drive so that all important data and information stored on the device are properly protected from unauthorized or malicious users. All data are transmitted between the app and the OUHSC secure REDCap server using a secure, encrypted transmission

(SSL/HTTPS). REDCap has been used by several institutions in Lao. The tablets are password protected, encrypted, and can be remotely wiped if lost.

- All data related to participants will be identified only by the UIN. A master list of participant UINs linked to participant names will be stored in locked file cabinets in locked study offices at SH or CH. Access to the master list will be limited to those with privileges. After completion of the study and data analysis, the identification file will be destroyed.
- Participants will not be identified in any public reports or documents. In qualitative component reports, if any, only participant initials or random initials will be used for quotations. In the trials, only aggregate data will be reported and released. At no time will individual names appear in any report, article, or manuscript related to the study.
- To minimize risks related to participant information potentially being disclosed via the use of smartphones, the following features are designed to ensure the security of the assessment data:
    - The data stored on the smartphone device is in a SQLite database in a sandbox environment, where read/write operations are only available through the programming application (i.e., no file or output is readable to end users).
    - A 10-character password (only known to researchers) is required to authenticate the current user before data can be manually accessed on the smartphone.
    - Encrypted smartphone data will be automatically sent to our OUHSC mHealth Shared Resource secure servers multiple times per day.
    - The web browser application linking the investigator's computer to the database uses HTTPS protocol (SSL certificate with encryption), which will guarantee the protection of data transferred from the web browser to the backend database.
    - The backend database is hosted by the OUHSC mHealth Shared Resource in a secure setup.
    - Software will be downloaded onto each study phone so that phones can be remotely wiped if lost.
- During the consent process, participants will be informed of the potential for psychological distress or discomfort associated with unintentional disclosure of personal information to non-study staff, and the nature of the questions to be asked will be made clear.
- Participants will be informed of the safeguards in place and encouraged to contact investigators at any time to discuss any confidentiality concerns that arise.

Protection against Coercion: All recruitment contacts will emphasize the voluntary nature of participation. Consent materials will clearly state that participants recruited for the trial will be randomly assigned to 1 of 2 groups and that participation in the study may not be personally beneficial.

Protection against Assessment-Related or Intervention-Related Discomfort:

The potential for discomfort associated with being asked personal questions regarding sensitive topics will be minimized in the following ways:

- Participants will be informed of the nature of questions to be asked and topics covered; participants can decline participation if such topic areas are known to be personally uncomfortable.
- Only measures that have been validated or used in prior studies will be used or will be adapted for use in this study. None of the proposed instruments have been known to evoke serious emotional reactivity.

- The use of self-administration for the assessments on a tablet or phone may help participants feel more comfortable in answering sensitive questions.
- Participants can refuse to answer any questions that they do not wish to answer.
- Participants who become distressed by answering questions will be given resources to access help.
- Participants will be reminded during the consent process that they may contact the research staff with any questions or concerns that arise during their participation.
- Participants may choose to discontinue participation at any time.

Those who experience a skin reaction from nicotine patch use will be instructed to move the site of the nicotine patch each day. Additionally, participants will be instructed to wait at least 7 days before using the same site for patch placement. To minimize nausea, participants will be instructed not to smoke while using the patch. If smoking relapse occurs, the participant will be instructed to stop using the patch. Participants experiencing distressing dreams or other sleep interference will be instructed to remove the patch before bedtime. If a severe skin reaction develops, the participant will be instructed to discontinue patch use. Use of the patch should reduce the severity of withdrawal-related symptoms. Withdrawal symptoms are generally short-lived and typically last no more than 2 weeks after smoking cessation. Patches will be dispensed under the supervision of a health care provider.

K3. Potential Benefits of the Proposed Research to Human Subjects and Others

Tobacco smoking is among the leading causes of morbidity and mortality in low- and middle-income countries. Smoking cessation treatment offers tremendous potential to prevent smoking-related morbidity and to reduce overall mortality in this population. The risks to participants are small, and the health benefits of quitting smoking at the individual level are appreciable and well documented.

To our knowledge, no theoretically based tobacco treatment program is available in national public hospitals in Lao PDR. It is also unknown whether mHealth-based smoking cessation approaches that have efficacy in developed countries would be effective in low- and middle-income countries. The results of this study will help Lao governmental health officials implement a potential affordable and sustainable approach for smoking cessation for Laotians that may lead to widespread adoption and also be applicable to other health issues. Thus, this research has the potential to transform healthcare delivery throughout the country.

L. MULTIPLE SITES

Not applicable.

M. STATISTICAL METHODS

Descriptive statistics will be used to assess ***feasibility*** of AT. Regarding ***preliminary efficacy*** of AT, we will use log-binomial regression with an intent-to-treat approach (i.e., missing=smoking) to compare the effect of the treatment on the dichotomous abstinence outcome at 12 weeks post-enrollment, controlling for selected covariates such as sex, education level, and/or baseline stress level. Secondary outcomes will be examined using appropriate linear and generalized linear mixed models with log-binomial and linear regression for binary and continuous variables, respectively. Given the preliminary nature of the RCT, we do not expect to have sufficient power for full hypothesis testing. However, from our previous work, we anticipate that the abstinence at the 12-week follow-up will be 8% in the SC group. With 40 participants in each group, we will have 80% power to detect a difference as small as 20% in

smoking abstinence rates between groups (α=0.05, one-tailed, unadjusted).

Mixed methods data analysis. At the 3-month follow up assessment, we will use additional open-ended questions at the end of the assessment to explore why and how the participants did or did not successfully quit smoking and stay abstinent. Specifically, for participants who were biochemically confirmed abstinent, the questions will focus on what motivated them to quit and how they overcame challenges or barriers to stay abstinent. For participants who were not abstinent, the questions will focus on why they did not or could not quit, what they underwent, what challenges or barriers they had, and what would help them quit in the future.

Two research team members will perform qualitative data coding with the aid of the R-QDA.[77] Discrepancies will be discussed to achieve intercoder agreement. Codes and quotations will be arranged into focused themes (i.e., thematic content analysis) to develop the mixed methods data inventory.[78] Next, we will examine quantitative (RCT) and qualitative data jointly, using the ***integration strategy of explaining*** with the intent to explore why participants could or could not quit and stay abstinent.[78,79] Mixed methods linked data, results, and meta-inferences will be presented in visual joint displays,[79] similar to our previous publication.[80]

N. DATA AND SAFETY MONITORING PLAN

The PI (Dr. Bui) and site PI (Dr. Xangsayarath) will be responsible for all data monitoring and for compliance with all federal, OUHSC IRB, and Lao IRB policies and procedures regarding monitoring progress, safety, reporting of unanticipated problems or adverse events, and assuring that actions resulting in suspension of the study are reported.

Unanticipated problems

The PI will inform the OUHSC and Lao IRB within five (5) business days of discovering any unanticipated problems (both internal and external) involving risks to participants and others.

Serious adverse events

A serious adverse event is defined as follows: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, a congenital anomaly/birth defect, or a medically significant event. Risks of participation will be continually monitored and appropriate measures implemented in cases of unforeseen adverse events. If a serious adverse event occurs, the PI will notify the IRB and the designated program person at the NCI in writing. These events will be reported regardless of whether they appear to be related to study procedures.

Given the non-invasive, minimal risk nature of the proposed research, we anticipate no serious adverse events related to the interventions or the study procedures. The types of adverse experiences that may occur, if any, will focus on the possible distress associated with self-interviews during data collection or on the use of nicotine patches. We have included procedures to minimize these risks (see section K above).

Adverse Experiences Associated with Self-Report

The trials will involve the use of assessments that could reveal sensitive information (e.g., mood disturbance, substance use). The instruments are not used to communicate psychiatric diagnosis to the participant and procedures are in place to protect participant confidentiality. Possible resolutions for this type of adverse experience include referring participants to their primary care physicians, and/or other physicians, and/or other mental health providers. Other procedures to minimize this type of adverse experience are described in the section K above.

Adverse Experiences Associated with the Nicotine Patch

Adverse experiences associated with the nicotine patch are almost always of a mild nature. Potential risks arising from use of nicotine patch therapy are mostly limited to nausea, erythema, and other dermatologic reactions. Procedures to minimize this type of adverse experience are described in the section K above. The incidence of side effects with the patch is small and can be locally treated or reversed with discontinuation of the patch. The risk of nicotine toxicity is extremely low. Appropriate warnings about not smoking while using the patch will be issued each time patches are dispensed. Management of AE's are done in accordance with standards of clinical practice and almost always are relieved by a reduction in dose, or although rarely necessary, discontinuation of patch use.

Adverse Experiences Associated with Nicotine Abstinence/Withdrawal

Participants may also experience nicotine abstinence/withdrawal effects. These effects may include irritability, difficulty concentrating, insomnia, anxiety, dysphoria, and increased hunger. None of these effects results in serious adverse events.

COVID-19 Risk Mitigation Plan

The below actions will be implemented to mitigate the risk of COVID-19 transmission and acquisition:

- In general, the Lao research team and US investigators in Lao PDR will follow COVID-19 prevention plan/guidance of the Ministry of Health of Lao PDR.
- Body temperature check: Before in-person interviews, body temperature of research staff and participants will be measured using a portable non-contact infrared digital thermometer. Research staff's body temperature will be measured once per day before the first interview. Persons with a temperature >38.5^{o}C will not be allowed to participate in the interviews and will be advised to seek further health care.
- Masking: All research staff and participants will be provided surgical-style masks and will be required to wear masks during in-person interviews.
- Hand washing: Research staff and participants will be asked to wash their hands before and after the interviews.
- Wearing gloves: Research staff will be required to wear gloves when direct physical contact with research participants is needed, discard gloves after contact appropriately, and wash hands.
- Social distancing: Research staff and participants will be required to maintain social distancing of 6-feet (2 meters) in all directions unless necessary to conduct intervention or measures.
- Disinfection: Research areas and tools, including rooms, tables, chairs, and tablets will be appropriately disinfected as recommended by the Ministry of Health of Lao PDR. Disinfecting will take place before the first participant, between participants, and after the last participant. Inexpensive supplies such as pens, small notebooks, or participants' folders will be given to participants without reuse/recycling.
- The Directors of the participating hospitals and of the NCLE (i.e., site PI) will be informed if the research staff becomes aware of a team member or a participant who tests positive for COVID-19.
- As the nature of COVID-19 remains dynamic, the NCLE will regularly evaluate this COVID-19 prevention plan and revise the plan if necessary.

O. DATA SHARING

The US and Lao investigators have equal rights to access to study data.

All qualitative data will be deidentified during the verbatim transcribing process and translation to English. Deidentified data will be transferred to the PI in encrypted files.

Quantitative data collected by REDCap program will be transmitted between the REDCap app and the OUHSC secure REDCap server on a daily basis using a secure, encrypted transmission (SSL/HTTPS). REDCap has been used by several institutions in Lao. The tablets with REDCap mobile app are password protected, encrypted, and can be remotely wiped if lost.

Quantitative data collected by our Insight app on smartphones will be automatically encrypted and will be automatically sent to our OUHSC mHealth Shared Resource secure servers whenever there is active internet (4G) connection. The web browser application linking the investigator's computer to the database uses HTTPS protocol (SSL certificate with encryption), which will guarantee the protection of data transferred from the web browser to the backend database. The backend database is hosted by the OUHSC mHealth Shared Resource in a secure setup.

Data storage, or data transfer if there is a request, will follow all OUHSC's requirements for data security. In all components of the research project, participants will be assigned unique identification numbers, and this identification numbers will be used in all data transfer and data analysis. When data sharing is requested, de-identified data files will be transferred on a password-protected and encrypted drive and will be maintained on institutional servers with appropriate antivirus software. Final de-identified data files will be maintained by the PI at OUHSC, and all other copies of data files will be deleted after the publication of outcome papers.

P. CONFIDENTIALITY

Protection against Confidentiality Breach: Confidentiality will be maintained for all data and contact information. To protect against the risk of a confidentiality breach, the following steps will be taken:

- REDCap will be used to collect and manage information for most procedures, including screening eligible participants, administering in-clinic assessments at baseline and follow-ups, and capturing participants' information from medical records. REDCap is a secure web-based application designed to comply with all HIPAA regulations. Data will be collected by participants (e.g., self-interviews for baseline assessment) or by research staff (e.g., screening or reviewing medical records) on tablets using the REDCap Mobile App. Each participant will be given a unique identification number (UIN) in this study, and the UIN will be used in all data collection procedures that are managed by REDCap. The REDCap Mobile App employs encryption at-rest on the mobile device's hard drive so that all important data and information stored on the device are properly protected from unauthorized or malicious users. All data are transmitted between the app and the OUHSC secure REDCap server using a secure, encrypted transmission (SSL/HTTPS). REDCap has been used by several institutions in Lao. The tablets are password protected, encrypted, and can be remotely wiped if lost.
- All data related to participants will be identified only by the UIN. A master list of participant UINs linked to participant names will be stored in locked file cabinets in locked study offices at SH or CH. Access to the master list will be limited to those with privileges. After completion of the study and data analysis, the identification file will be destroyed.

- Participants will not be identified in any public reports or documents. In qualitative component reports, if any, only participant initials or random initials will be used for quotations. In the trials, only aggregate data will be reported and released. At no time will individual names appear in any report, article, or manuscript related to the study.
- To minimize risks related to participant information potentially being disclosed via the use of smartphones, the following features are designed to ensure the security of the assessment data:
    - The data stored on the smartphone device is in a SQLite database in a sandbox environment, where read/write operations are only available through the programming application (i.e., no file or output is readable to end users).
    - A 10-character password (only known to researchers) is required to authenticate the current user before data can be manually accessed on the smartphone.
    - Encrypted smartphone data will be automatically sent to our OUHSC mHealth Shared Resource secure servers multiple times per day.
    - The web browser application linking the investigator's computer to the database uses HTTPS protocol (SSL certificate with encryption), which will guarantee the protection of data transferred from the web browser to the backend database.
    - The backend database is hosted by the OUHSC mHealth Shared Resource in a secure setup.
    - Software will be downloaded onto each study phone so that phones can be remotely wiped if lost.
- During the consent process, participants will be informed of the potential for psychological distress or discomfort associated with unintentional disclosure of personal information to non-study staff, and the nature of the questions to be asked will be made clear.
- Participants will be informed of the safeguards in place and encouraged to contact investigators at any time to discuss any confidentiality concerns that arise.

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