RESEARCH PROTOCOL

(Last updated: July 15, 2020)

Title of Project: Mobile Health Technology for Personalized Tobacco Cessation Support in Laos (Support Laos)

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Abstract

Tobacco use remains the leading cause of preventable morbidity and mortality in Lao People's Democratic Republic (Lao PDR). This project adapts our theoretically and empirically based mobile health (mHealth) technology to help Lao people quit smoking cigarettes. This mHealth approach includes a fully automated, interactive, personalized, smartphone-delivered intervention for behavioral treatment, delivered through our Insight™ platform. The proposed project includes 2 main phases. In the R21 Phase, we will use formative research methods to adapt our intervention content to the sociocultural context, language, and communication styles of Laotians. In the subsequent R33 Phase, we will conduct a randomized controlled trial to evaluate the efficacy of our mHealth intervention and technology. In the trial, adult smokers of both sexes will be recruited through 2 large hospitals: Setthathirath Hospital in Vientiane and Champasak Hospital in Champasak Province. Participants (n=500) will be randomized to either Standard Care (SC; n=250) or Automated Treatment (AT; n=250) group. SC consists of brief advice to quit smoking delivered by research staff, self-help written materials, and a 2-week supply of nicotine replacement therapy (transdermal patches). AT consists of all SC components plus a fully automated smartphone-based treatment program that involves interactive and personalized proactive messages, images, or videos.

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 Champasak Hospital—are under supervision/management of the Ministry of Health of Lao PDR and have assurances relying upon the NECHR IRB#1 (FWA00026579 and FWA00028083, respectively).

A. SPECIFIC AIMS

The specific aims are to:

- Aim 1 (R21 Phase): Adapt the AT content to the Lao sociocultural context and communication styles.
- Aim 2 (R33 Phase): Conduct a randomized trial to evaluate the efficacy of AT. *Hypothesis*: At the 12-month 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.

The US and Lao researchers are committed to a long-term partnership beyond this proposed project, with the goal of sustaining an affordable nationwide mHealth intervention for tobacco cessation and for other health promotion programs in Lao PDR. We have involved Lao stakeholders at national institutions, including national/regional hospitals, National Tobacco Control Committee (NTCC), and the Ministry of Health (MOH) in this project. If our findings indicate that AT is effective, this collaboration with influential Lao governmental agencies will facilitate wide-scale dissemination to other hospitals/clinics across the country. Thus, the project has the potential to transform healthcare services for tobacco treatment throughout the country and, ultimately, to significantly reduce tobacco-induced morbidity and mortality. The project will also contribute to creating a knowledge base for mHealth research applications in LMICs and advancing mHealth research capacity in Lao PDR (e.g., the use of mHealth tools for adaptive personalized interventions and analyzing ecological momentary assessment data).

B1. BACKGROUND AND SIGNIFICANCE

Globally, tobacco causes approximately 6 million deaths each year, of which 80% occur in low- and middle-income countries (LMICs).[9,10] Tobacco use is the most important modifiable risk factor for cancer prevention and is a leading preventable cause of death[9]; smoking prevention and cessation are the most impactful and cost-effective interventions among the many recommended evidence-based preventive health services.[11] Despite the need, cessation treatments in LMICs are often unavailable or unaffordable for most people.[9]

Of 7 million citizens in Lao PDR, 51% of men and 7% of women smoke tobacco.[1,12] 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;***[12,13] 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).[2] 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.[14] Active mobile-broadband subscriptions grew extremely rapidly from 4% in 2007 to 56% in 2017, without signs of faltering.[14] 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.[15] 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.[15] 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.[16] In recent years, mobile-cellular subscription rates in Lao PDR ranged from 56%–68%;[15-17] half of these included mobile-broadband subscriptions.[14] 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,[14] 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)[18] 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.[19] Short message service (SMS) is also used in a real-time reporting system for vaccine administration and monitoring.[20,21] 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.[3,4] A thorough economic analysis demonstrated that a mobile phone text messaging intervention for smoking cessation is cost-effective.[5] Indeed, mobile phone-delivered text messaging has been identified as one of the most affordable interventions[8] and has been endorsed and used by several international organizations, including the WHO, in their global tobacco control efforts.[6,7] 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]

Summary. Cigarette smoking represents a major public health problem in LMICs including Lao PDR. However, both the literature and our discussions with key stakeholders in Lao PDR reveal a lack of national smoking cessation treatment programs. Our proposed study will evaluate our already developed cutting-edge mHealth intervention – Automated Treatment (AT) – for smoking cessation in Lao PDR. Given AT's potential as a feasible, scalable, and highly affordable stand-alone intervention, our approach is ***appropriate for use in LMICs*** and could

substantially reduce smoking prevalence and smoking-related morbidities in the Lao population. The sustainability and potential for widespread adoption are enhanced by the direct involvement of Lao PDR governmental stakeholders at multiple institutes. Furthermore, it is largely unknown whether effective cessation interventions from high-income countries are transferable and applicable to LMICs;[9] thus, our proposed work will ***address this gap in knowledge***. Finally, the US-Lao collaborative work and capacity building activities in this project will ***advance mHealth research capacity and mHealth use*** in Lao PDR. Therefore, the proposed project is consistent with the objectives of this R21/R33 funding mechanism.

B2. INNOVATION

Our mHealth Technology Shared Resource (Director: Dr. Businelle, co-I) has developed the novel HIPAA-compliant Insight™ mHealth platform (*see Appendix*). The Insight™ platform empowers researchers to ***build, test, and launch secure technology-based assessment and intervention tools*** for various health behaviors or issues. The versatile Insight™ platform enables researchers to track momentary changes in key variables from multiple data sources (i.e., phone-based surveys, sensor data, geolocation data) in near real-time and use this information to initiate interventions. The Insight™ platform has 2 primary components: a web-based Content Management System (Insight™ CMS) and an Insight™ app (a smartphone application shell). Once a project is created in the CMS, researchers can use the intuitive interface to select and use emerging approaches in research (e.g., ecological momentary assessments [EMA] or just-in-time adaptive intervention), features (e.g., facial recognition, activity monitoring, and remote carbon monoxide [CO] monitoring), assessment types, and intervention delivery options that are needed for the project. Currently, the Insight™ platform has been utilized in 40 projects focusing on diverse health behaviors, such as smoking cessation, alcohol cessation, sedentary behavior reduction, medication adherence, and linking homeless adults with case managers. Each project is firewalled from all other projects.

In this project, US and Lao investigators will jointly use the Insight™ platform to deliver and manage AT. This use of Insight™ is innovative in several aspects. Insight™ allows our AT to ***function autonomously*** and minimizes human involvement, making the approach very affordable for large-scale implementation in LMICs. Using Insight™ CMS, investigators can easily load all intervention content and assessments and preschedule delivery dates and times. Through one-click buttons in the Insight™ app, participants can call or message project staff if they have questions or need assistance. During large-scale implementation of AT beyond this project, Lao researchers could also use the Insight™ CMS to modify the intervention (e.g., adding relevant treatment content in Lao or change assessment frequency). In other words, Lao researchers can directly manage AT whenever and however they wish without knowledge of programming languages.

The use of Insight™ to deliver AT has several other advantages over the traditional SMS approach. While an SMS intervention would work on virtually all phones in Lao PDR, it requires an active cellular network connection. Our Insight™ app will automatically deliver all interventions and assessments as prescheduled, ***with or without an active connection***, thus ensuring timely and reliable AT delivery throughout the 6-month treatment period. Similarly, Insight™ can deliver preloaded video content as needed while traditional SMS can only deliver a link and requires an active connection to view the media. Most importantly, Insight™ enables complex built-in algorithms and branching logic, allowing us to create and deliver dynamically

and individually tailored treatment content. Specifically, based on participant responses to baseline and in-clinic assessments, Insight™ will automatically select intervention content ***personalized*** to each individual's characteristics, including biological sex and health conditions (e.g., lung or cardiovascular diseases). The weekly assessment will capture each individual's thoughts, feelings, and behaviors (e.g., distress or self-efficacy) and behavioral phases (e.g., cessation vs. maintenance) following the Phase-Based Model.[24,25] ***Utilizing these near real-time data, Insight™ will automatically select and schedule delivery of adaptive intervention content*** for the next week. Such a complex level of personalization and data-driven intervention is not possible with traditional SMS without intense human involvement. Because of the clear advantages, we propose to use the Insight™ app, although the Insight™ platform can deliver messages and links via SMS. While the use of Insight™ and smartphones may currently exclude some very low-income smokers, data shows that smartphone ownership is nearing ubiquity globally, including in Lao PDR (particularly, by the time the project is completed in 2025). Thus, our proposal to use Insight™ and smartphones for AT delivery represents an attempt to utilize powerful technology while maximizing reach and impact.

In addition to addressing a critically important public health problem in Lao, the proposed project will allow our Lao-based investigators to become familiar with the Insight™ system and its capabilities. The Insight™ platform can be used to intervene upon health behaviors other than smoking cessation. In future collaborative studies, we envision evaluating advanced Insight™ features for other integrated healthcare services for Laotians (e.g., using facial recognition and a pillbox sensor to monitor medication adherence in smokers with tuberculosis). Lao researchers may also initiate Insight™-based intervention research tailored to the needs of their nation in collaboration with the US team. Our project will provide a strong foundation for ***future continued applications of mHealth intervention research*** in Lao PDR.

Several other aspects of the proposed work are innovative. First, our AT is theoretically and empirically based. While several theory-based intervention studies (including our own) have been conducted in developed nations, efforts to adapt and disseminate these interventions to LMICs, such as Lao PDR, are lacking. In fact, there is no publication of theoretically based smoking cessation research in Lao PDR. Even in the US, where numerous smartphone apps for smoking cessation are available, only 4% of the top 50 apps in leading app stores have any scientific basis.[22] Our proposed project is the first effort in Lao PDR to adapt a mHealth intervention for smoking cessation that is theoretically and empirically based and culturally tailored. Second, this project is a close collaboration between US investigators and Lao stakeholders at many institutions, including national/regional hospitals, the MOH, and the NTCC (see *Research Team*). The US and Lao researchers are ***committed to a long-term partnership to build and sustain a national mHealth treatment program for tobacco cessation in Lao PDR***. This committed partnership will provide critical infrastructure to support the future widespread adoption and sustainability of AT in Lao. Finally, through collaboration and capacity building activities, this project will be the first to train Lao investigators in EMA methodology and will strengthen overall mHealth research competencies in Lao PDR. In summary, the project will lay the groundwork for a sustained US-Lao mHealth research network that will support future high quality mHealth research projects in Lao PDR.

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.[1,26-32] 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),[33-38] tobacco health risk communication (Dr. J. Vidrine),[39-42] mHealth methodology (Dr. Businelle),[43-46] and biostatistics (Dr. Frank-Pearce).[44,45,47,48] Dr. Xangsayarath is the Vice 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.[1] Drs. Keopaseuth and Keothongkou are Directors of the Setthathirath Hospital and Champasak Hospital, respectively, where the proposed R33 Phase will be implemented.

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.[32,50] 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

D1. Overview

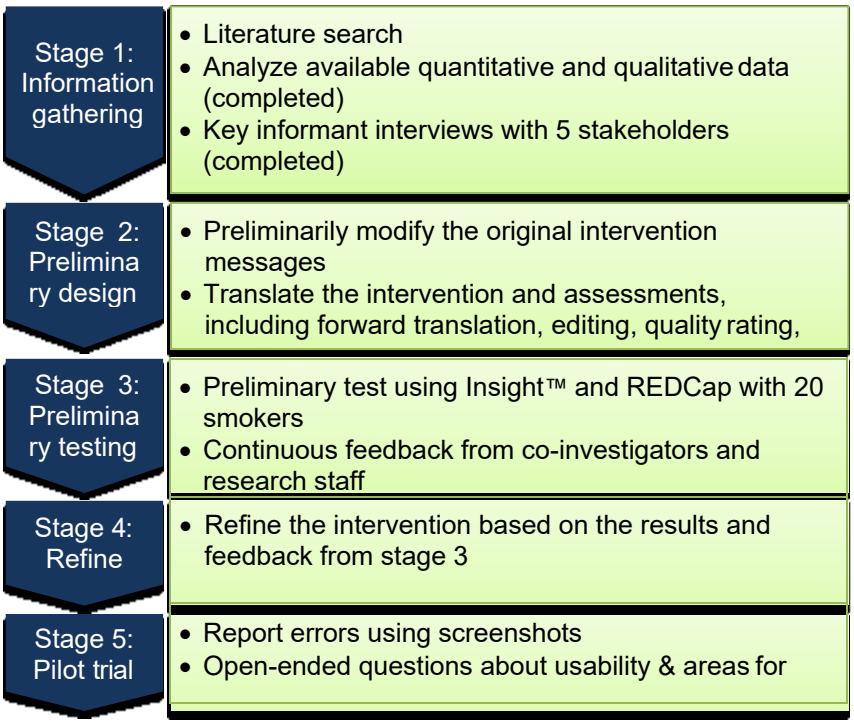
This proposed project includes 2 main phases: the R21 and the R33. In the R21 Phase, we will use various formative research methods to validate and adapt our intervention content to the sociocultural context, language, and communication styles of Laotians. In the R33 Phase, we will conduct a 2-group RCT to compare the efficacy of 2 smoking cessation interventions: smartphone-delivered automated treatment (AT; n=250) versus standard care (SC; n=250).

D2. R21 Phase (2 years, July 2020 – June 2022): Adaption of the AT intervention content

Because we will adapt an existing AT intervention that is theoretically-based and has demonstrated efficacy in our previous RCTs, we will use the cultural adaptation of evidence-based interventions approach.[51,52] Although several models have been proposed to guide cultural adaptation, there is considerable consensus that cultural tailoring can be organized into 5 stages: information gathering, preliminary design, preliminary testing, refinement, and final trial.[52] Figure 1 summarizes our R21 research activities.

In stage 1, formative research, including literature searches, quantitative results, and qualitative methods (e.g., key informant interviews) are often conducted to determine how well an original intervention will fit the needs and preferences of the target population. We have already partially completed this stage. Specifically, we have conducted literature searches, analyzed quantitative results of the NATS,[1] and discussed our intervention approach with 5 key stakeholders (at the MOH, NTCC, and University of Health Sciences in Lao PDR). Information gathered from these activities helped us to shape this proposed project. For example, NATS data show that ~90% of male tobacco users smoke cigarettes;[1] thus, we will adapt the AT intervention to target cigarette smokers first. MOH and NTCC stakeholders confirmed that the AT has great potential regarding scalability and sustainability. NTCC's previously developed materials in Lao for smoking cessation support will be used for the SC group or to adapt our intervention content library.

Figure 1: Adaption of the AT intervention content



In this project, we will conduct in-depth interviews with 30 healthcare providers at participating hospitals to learn more about how they typically motivate patients to quit smoking and stay abstinent. They can develop intervention messages if they wish or pinpoint the sources of treatment content that they use. We will use purposive sampling to select 15 providers from each hospital, 15 of each sex, and ensure the sample is diverse with regard to age and specialty. *Inclusion criteria* for all healthcare providers in the R21 Phase include: 1) age ≥18 years; and 2) the ability to provide written informed consent to participate. Also, we will conduct 8 focus group discussions with 40–60 patients who smoke (5–8 persons/group, 4 groups/hospital) to identify additional factors that motivate patients to quit smoking and stay abstinent, barriers to quitting, and strategies to overcome these barriers. We will use purposive sampling to select a diverse sample with regard to age, residence (urban vs. rural), disease type, and cessation phase, per the Phase-Based Model (PBM; see *Conceptual Framework*). *Inclusion criteria* for all patients in the R21 Phase (except in stage 5 below) include: 1) age ≥18 years; 2) self-reported current combustible cigarette smoking (smoked ≥100 cigarettes in lifetime and currently smoke ≥1 cigarette/day); 3) planning to quit in the next 6 months or having actually made a quit attempt; and 4) the ability to provide written informed consent to participate. We will conduct separate group discussions for men and women (2 groups for each sex at each hospital). For all qualitative components in the R21 Phase, we will use open-ended questions. All interviews/discussions will be recorded using a digital voice-recording app on an encrypted smartphone and will be transcribed verbatim. Qualitative data will be analyzed using thematic content analysis with the aid of the R-based Qualitative Data Analysis software package.[53] Themes will be based on the purpose of each component and on theoretical constructs of the PBM.

In stage 2, we will integrate information gathered in the first stage to modify the original intervention. For example, using literature search and qualitative findings from our Cambodian pilot study, we have expanded our treatment content library to include strategies for coping with craving/urges that are commonly used in Southeast Asian culture (e.g., chewing on ginger/lemon, chatting with friends via apps, or playing e-games on phones to keep hands busy). The original English treatment content library and NTCC's available materials are mainly text based. For videos originating in the English library, US and Lao investigators will review, discuss, and select the ones that are culturally appropriate for use in Lao PDR (e.g., videos that

do not contain US-specific characters or contexts). Scripts of the selected videos will be translated as described below, and the videos will be dubbed by native-Lao speakers).

Also at this stage, we will translate all English intervention materials and assessments that will be used in the R33 Phase to Lao, mirroring the WHO's recommended methodology[54,55] that we used in our pilot study in Cambodia. First, a health scientist, whose native language is Lao, will lead the forward translation process, focusing on conceptual (vs. literal) meaning and comprehensible language for the broadest audience. Second, a more senior bilingual health expert will review the translation, discuss disagreements with the forward translator, edit, and finalize the forward translation. Third, 2 other bilingual health professionals will independently rate the quality of the translation on 5 dimensions: conceptual equivalence, clarity in meaning, comprehensibility, use of common simple language, and cultural appropriateness. Any discrepancies will be discussed to reach consensus on translation or editing. Fourth, we will conduct 6 panel discussions (1 with female smokers, 1 with male smokers, and 1 with mixed-sex healthcare professionals at each participating hospital; 5-7 panelists per group). This step aims to evaluate material comprehensibility as well as linguistic and cultural appropriateness for the target populations, particularly to identify linguistic differences by regions (north vs. south) in Lao PDR and to find and use common words. Fifth, 2 other bilingual health professionals will independently backward translate the materials into English. Finally, the PI and site-PI will independently review and rate the backward-translations for conceptual equivalence with the original English versions.

In stage 3, we will load the intervention content onto the Insight™ platform and assessments into REDCap and will preliminarily test them (on smartphones/ tablets) with 20 patients who smoke (10 male, 10 female). Additionally, we will systematically document continuous feedback from local investigators and staff members who implement stages 2 and 3 for adaption refinement. In stage 4, we will refine the intervention based on the results and feedback from stage 3. Critical changes at this stage (e.g., major deviations from the original intervention) will only be made in consultation with the leadership team.

Stage 5 will be a 3-month pilot efficacy trial with 50 patients. Activities at this stage will mirror the full efficacy trial in the R33 Phase, except that only 50 patients will be recruited and treatment will last 3 months. In addition to the efficacy outcomes, we will collect data for further adaption and refinement. Specifically, at the baseline, we will instruct participants to take screenshots of the phones and ask them to do so whenever they see a message that they do not understand, that has an error, or that needs revision. We will ask participants to send us these screenshots together with descriptions of issues via Insight™ or e-mails. At the follow-up, we will check for and discuss all stored screenshots with participants to elicit their suggestions for revision, and we will ask AT participants open-ended questions regarding usability and areas for improvement in the AT.

D3. R33 Phase (3 years, July 2022 – June 2025): Conduct a RCT to evaluate the efficacy of AT

Overview. Participants will be patients recruited through 2 large hospitals in Lao PDR. Consenting participants will be randomized to one of the 2 study groups: Automated Treatment (**AT**; n=250) and Standard Care (**SC**; n=250). Participants will complete in-clinic assessments at baseline, and at 3, 6, and 12 months following study enrollment (*Figure 2*). Participants will also complete brief weekly assessments via smartphone.

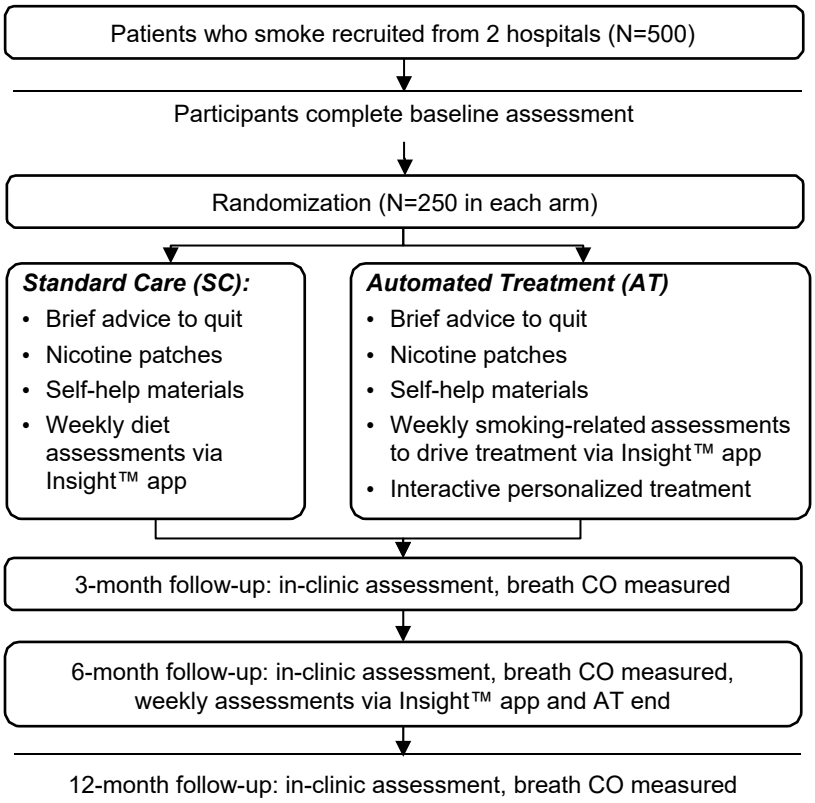
Design considerations. Several aspects of the project, as described below, were carefully

considered prior to deciding on the proposed design.

Provision of NRT. We considered a 2X2 fully crossed randomized design to differentiate the effects of pharmacological support (NRT) versus behavioral treatment (AT). However, NRT helps address nicotine withdrawal/craving[25,56] and the US Public Health Service Guidelines state that NRT should be considered the minimal standard of care.[57] Thus, it would be unethical to have a study group without NRT in a large trial. On the other hand, providing too much NRT may mask the effect of AT and affect the sustainability of the program. Most quitlines in the US provide a minimum of a free 2-week starter kit of NRT and we will follow this practice.

Provision of smartphones. We considered using a more real-world approach, in which only individuals who already owned smartphones would be eligible for study entry. However, we decided that loaning smartphones to those who either do not own or own an incompatible smartphone would actually provide a more thorough and realistic estimate of AT's potential. This is especially true given the trend in Lao smartphone ownership over the past few years which indicates that ownership will be nearly ubiquitous in the near future. In our Cambodian pilot study, 88% returned the project phones after 2 months.

Figure 2: Trial schema



Oversampling female smokers. We acknowledge the importance of ensuring that our mHealth-based AT program works well for women. Thus, in the R21 Phase, we will recruit equivalent numbers of male and female smokers for qualitative interviews/discussions. However, given the limited timeframe and budget of the R33 Phase, we must guarantee a sufficient sample size to demonstrate the efficacy of AT in at least the majority group of smokers (i.e., males) if subgroup analysis is needed. Thus, we cannot oversample female smokers but we will ensure that female smokers are represented in a manner that aligns with smoking prevalence in the real-world. Specifically, because the male to female smoking prevalence ratio in the general population is ~7 (51%:7%),[1] we propose to recruit a sample that includes 15% (n=75) females. By doing so, we recognize that we may not have sufficient power to detect a difference in the primary outcome in the female subsample. However, given that little is known about the factors associated with smoking cessation in Laotian females, this proposal will provide valuable information that may inform future research efforts.

Conceptual Framework for AT. Our AT intervention is based on Phase-Based Model

(PBM), a theoretical framework that is specific to smoking cessation.[24,25] PBM partitions the cessation process into 4 phases: motivation, preparation (pre-cessation), cessation (quit date to 4 weeks post-quit), and maintenance (up to 6 months post-quit); this RCT focuses on the latter 3 phases. PBM helps identify challenges/opportunities that smokers face at each phase, explains underlying phase-specific mechanisms, and facilitates selection of intervention components and measures. Using data from weekly assessments, the proposed AT intervention will ***dynamically*** target several putative mechanisms, mainly those that are relevant across phases and have been reliably associated with long-term abstinence in previous studies: withdrawal/craving, motivation to quit, positive/negative affect, coping with stress and urges, and self-efficacy.[25,58-61]

Withdrawal/Craving. As explained above, NRT provision helps address nicotine withdrawal/craving,[25,56] and increases quit rates.[57] AT will also promote skills to further reduce and cope with withdrawal and craving.

Motivation to Quit. Substantial evidence underscores the critical role of motivation in initiating and successfully maintaining change.[62-65] Evidence also demonstrates that motivation for change can fluctuate rapidly.[66] For example, 41% of US smokers report that their motivation to quit smoking changes daily,[67] and half or more quit attempts are unplanned versus planned,[68,69] consistent with the PBM's tenet that motivation is dynamic. Empirical data indicate that higher levels of intrinsic motivation were associated with readiness to quit and the maintenance of abstinence at 12-month follow-up.[65,70]

Stress, Negative/Positive Affect. These are important mechanisms to target in the preparation and cessation phases.[25,58] Stress and negative affect, measured in different ways, have a strong dose-response relationship with smoking-related acute events.[71] The magnitude and trajectory of stress/negative affect over time are powerful predictors of cessation,[58,72,73] as are individual differences in affective vulnerability.[74,75] Stress/negative affect are associated with relapse and poor treatment outcomes in numerous studies.[76-79]

Self-efficacy. Self-efficacy is a form of agency that is context and behavior dependent. In the context of smoking, self-efficacy is reflected in one's confidence to not smoke in different challenging situations[80] and is among the best predictors of smoking treatment outcomes[60,77,81-83] and relapse.[84] Therefore, the PBM posits self-efficacy as a key mechanism in cessation and maintenance phases.

Figure 3. Location of recruitment sites

Sites and participant recruitment. Participants (n=500) will be recruited from the patient populations at Setthathirath Hospital (SH) in Vientiane and Champasak Hospital (CH) in Champasak Province. Vientiane is the capital and the largest city of Lao PDR, while Champasak is the most southwestern province and borders Thailand and Cambodia (*Figure 3*). SH and CH are public general hospitals under Lao MOH supervision. In 2018, the Lao MOH and Japan International Cooperation Agency selected SH and CH to receive grant aid of approximately 1.7 million USD from the Government of Japan to increase their capacities in providing high-quality medical care and services.[85] The grant supports improved facilities (e.g., construction of new buildings/rooms) and equipment (e.g., computed

tomography scan and computers) to help the hospitals serve more patients in the region. The goal of this capacity enhancement is to achieve universal health coverage, defined as coverage such that all people receive appropriate health promotion, and preventive, curative, and rehabilitative health services at affordable costs.[85] SH and CH are also among major implementation sites for several national disease control programs, including HIV, tuberculosis, and severe acute respiratory syndrome. These missions position the 2 hospitals as ideal venues to offer smoking cessation treatment, and the improved facilities and resources afford a solid foundation for AT adoption and implementation.

SH is a national hospital (i.e., at the top/central level in Lao PDR health system). Each year, SH serves approximately 20,000 inpatients and 90,000 outpatients from all over Lao PDR, mostly from the north and central regions. CH is the largest and the top-referral hospital in the southern region. CH serves patients from all nearby provinces, of which the total population is approximately 1.5 million people.

All non-emergency patients coming to SH and CH first go to a reception desk to receive a queue number and a basic medical form. A flyer that introduces this study will be attached to the basic medical form. Additionally, we will proactively recruit patients at the Respiratory Disease Screening Units (RDSU) and departments/clinics specializing in women's health (e.g., Gynecology, and Breast and Gynecologic Cancer). Due to the national organization and implementation of NCLE's disease control programs, all patients visiting SH or CH with respiratory symptoms are first examined at the RDSU for type of disease, severity, and whether the disease is included in a national disease control program (e.g., tuberculosis or severe acute respiratory syndrome). Patients are then referred to appropriate departments/clinics or disease control units. The RDSUs at SH and CH see about 40 and 20 patients daily, respectively. Of these, 70% are men; 60%–70% of male patients smoke cigarettes (no estimate available for women).[86,87] Research staff will proactively screen as many patients visiting the RDSU as possible for eligibility and invite eligible individuals to participate. Research staff will also proactively screen as many women visiting the women's health clinics as possible to enroll the target number of female smokers (n=75). Study protocols and procedures will be developed in Lao to standardize all research activities across sites.

Trial inclusion criteria include patients 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[88]). *Exclusion criteria* include 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. In our Cambodian pilot study at a clinic with fewer patients, 86% of identified eligible smokers consented to participate, and we recruited 2–5 participants per day; we expect a similarly high consent rate for this study. Together, SH and CH see >160,000 unique patients each year. Based on the smoking prevalence in the general population (51% in men and 7% in women), we estimate that approximately 40,000 male patients and 5,600 female patients at SH and CH will be current smokers. Assuming, conservatively, that only half of these smokers are eligible for the study and even if only half of eligible smokers want to participate, there will be 10,000 available male and 1,400 available female smokers in a one-year recruitment period. Thus, our goal to enroll 500 participants (<5% of eligible smokers) at SH and CH is highly feasible.

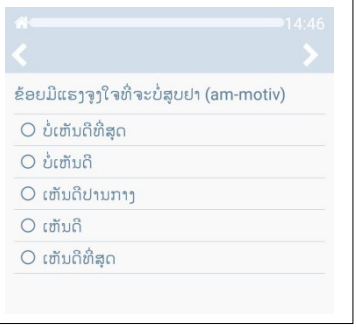
Baseline assessment. Enrolled participants will complete a 45-minute tablet-delivered baseline audio computer-assisted self-interview, managed and delivered by REDCap.[89,90] The use of REDCap will enhance both accurate data collection across sites and timely and secure data transmission. Research staff will assist participants complete the assessment if needed. Participants will be assigned to a treatment group using a form of adaptive randomization called minimization,[91-93] this ensures better group balance regarding participant characteristics and does not impose limitations such as empty or near-empty strata. Randomization variables include biological sex, nicotine dependence, and reading level. All participants will complete a brief training session on smartphone use and the Insight™ app. Smartphones will be loaned to participants who need them.

Treatment groups.

Standard Care (SC). Participants randomized to SC will receive brief advice to quit smoking delivered by research staff, NTCC's self-help materials (developed based on the WHO's "A guide for tobacco users to quit"[94]), and a 2-week supply of NRT (patches). SC participants will be asked to complete weekly 4-item smartphone-delivered assessments about their diet (see explanation in *Measures*) for a 6-month period.

Automated Treatment (AT). Participants in the AT group will receive the SC components (except the dietary assessments) plus proactive personalized messages/images/videos for smoking cessation. The AT content is adapted from the team's previous efforts (see *Preliminary Studies*), is informed by the R21 phase outcomes, and is designed to tap the theoretical mechanisms described in the PBM. That is, AT content is designed to increase motivation, self-efficacy, and use of coping skills, while reducing nicotine withdrawal symptoms and stress. AT will begin immediately after enrollment and continue for a 26-week period (about 2 messages/images/videos per day). The AT approach allows for ***several levels of personalization*** for each participant. First, at baseline, participants will be asked several questions about past quit attempts, preferred coping skills, and the presence or fear of specific health conditions. Treatment content tailored to these responses will be automatically delivered throughout the treatment period. Second, there will be different bins of treatment content for different cessation phases to ensure that AT targets critical mechanisms of each participant's PBM phase, which may dynamically change during treatment. Third, participants will be asked to complete brief (4 items) smartphone-delivered assessments during each week of the AT course. These questions will vary depending on each participant's phase (e.g., current level of intrinsic motivation for preparation or maintenance phases or smoking status in the past week and self-efficacy level for all phases). Treatment content (e.g., types and frequencies of messages) for the following week will be based on responses to these weekly assessments and participant phases (e.g., level of self-efficacy or past-week smoking status). Our team's previous work with disadvantaged populations has observed high adherence (76%) with weekly smartphone assessments across a 6-month timeframe.

Figure 4.



The Insight™ platform will be used to manage and deliver AT. Our pilot results in Cambodia demonstrate that Insight™ works very well in Southeast Asia; it is compatible with the GSM and 4G data networks, properly delivers messages and weekly assessments, and reliably collects and transfers data to our encrypted server. Our preliminary work also shows that the Insight™ platform and app work well with Lao script (*Figure 4*).

Measures and assessment strategy.

Table 2: Study Assessments

Variable Type	Measure	Baseline	Weekly*	In-clinic Follow-up (3-, 6-, & 12-mth)
Descriptors / potential moderators	Demographics; Health literacy[95]	X		
	Health conditions and comorbidities; Substance use[96,97]	X		X
	Dependence – Heaviness of Smoking Index[98]	X		
Adherence to treatment app	Duration of phone on/off; numbers of messages/images/videos delivered, opened, and marked as viewed; numbers of weekly assessments opened and completed; data syncing frequencies (manual and automatic)	Documented by digital date/time stamps in the Insight™'s activity log.		
Phase-Based Model mechanisms	Wisconsin Smoking Withdrawal Scale[99]	X		X
	Reasons for quitting (intrinsic, extrinsic)[65]	X		X
	Contemplation Ladder[62,63]	X	X**	X
	Kessler Psychological Distress Scale (K10)[100]	X	X**	X
	Positive and Negative Affect Schedule[101]	X		X
	Self-efficacy (related to smoking cessation)[84]	X	X**	X
Primary outcome	Smoking status (includes number of quit attempts, and days abstinent)[102]	X	X**	X
	Expired CO[102]	X		X

** Delivered via Insight™ app on smartphone; ** Brief versions of the scales.*

In-clinic assessments at baseline and at 3-, 6-, and 12-month follow-ups. Three types of data will be collected at each visit: ACASI data (*Table 2*) collected by the HIPAA-compliant REDCap program on a tablet, expired air CO assessed with a CO monitor (Vitalograph BreathCO) to verify smoking status biochemically, and medical record data (to collect clinical information, such as current diagnosed health conditions for AT personalization). The REDCap assessment will be administered at baseline (~45 minutes to complete) and at each follow-up in-clinic visit (~20 minutes). For measures that have not been validated in Lao, we will adapt them as described in the R21 Phase. Participants will be compensated $15 USD for each in-clinic visit.

Brief weekly smartphone assessments. Participants will be asked to complete weekly 4-item assessments via smartphone for 6 months, delivered by the Insight™ app. Participants in the AT group will receive 4 smoking-related questions (*Table 2*). Although these treatment-driving questions can be considered part of the AT, we will attempt to balance the effects of these weekly contacts between the treatment groups; SC participants will also be asked to complete a weekly 4-item assessment via Insight™ app with questions about diet. Responses will be temporarily stored on smartphones and will sync to our secure server whenever a connection is active; thus, we will have near real time access to the data. To carefully track participants' completion of weekly assessments and adherence, data plans will be provided for 6 months for both groups.

Primary outcome. The primary outcome is smoking status at 12 months post-enrollment. Abstinence will be defined as biochemically confirmed self-reported 7-day point prevalence abstinence with expired CO <6 ppm.[102] Secondary outcomes include 3- and 6-month abstinence. We will consider several other common outcomes, such as continuous and sustained abstinence, number of quit attempts, and length of abstinence.

Participant tracking and retention procedures. We will use various approaches to maximize our follow-up rate. These include: 1) reminders via phone calls, messages through the Insight™ home screen, and Insight™ push notifications before the follow-up visit; 2) offering follow-up assessments on different days/times to accommodate schedules; 3) collecting other phone numbers and home addresses of participants; 4) obtaining the names and phone numbers of at least 3 collaterals (e.g., relatives/friends) who can help locate the participant should the participant move or otherwise lose contact during the study; and 5) financially compensating participants for the time and costs associated with study participation (e.g., transportation, child-care). With these procedures applied in our Cambodian study, retention rates at 2 months were 100% for the AT group and 92% for the SC group. Thus, we expect a high retention rate for this proposed project.

E. CHART REVIEW

As described above, at the in-clinic assessments at baseline and at 3-, 6-, and 12-month follow-ups, 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 (R21 Phase):

- Inclusion criteria for all healthcare providers in the R21 Phase are: 1) age ≥18 years; and 2) the ability to provide written informed consent to participate.
- Inclusion criteria for all patients in the R21 Phase, except the pilot trial at stage 5, are: 1) age ≥18 years; 2) self-reported current combustible cigarette smoking (smoked ≥100 cigarettes in lifetime and currently smoke ≥1 cigarette/day); 3) planning to quit in the next 6 months or having actually made a quit attempt; and 4) the ability to provide written informed consent to participate.

- Inclusion criteria in the pilot trial at stage 5 include patients 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[88]).

Inclusion criteria (R33 Phase): All participants must be patients 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[88]).

Exclusion criteria (R33 Phase): 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.

I. GENDER/MINORITY/PEDIATRIC INCLUSION FOR RESEARCH

I1. Inclusion of Women

This project includes 2 main phases: the R21 Phase and the R33 Phase. In the R21 Phase, we will use qualitative methods (e.g., in-depth interviews and focus group discussions) to validate our intervention content to the sociocultural context, language, and communication styles of Laotians. We plan to recruit up to 110 participants for these qualitative components, with equivalent numbers of men and women. Then, we will conduct a pilot trial with 50 patients who smoke. We will recruit a pilot sample that mirrors the sample proposed in the main trial (R33 Phase). 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. Thus, we propose to recruit a sample that includes 15% (n=8) female smokers and 85% (n=42) male smokers in the pilot trial.

In the R33 Phase, we will conduct a full efficacy trial with 500 patients who smoke. 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. Thus, we propose to recruit a sample that includes 15% (n=75) female smokers and 85% (n=425) male smokers. 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

We will recruit up to 110 participants for qualitative components in the R21 Phase, 50 participants for the pilot trial in the R21 Phase, and 500 participants for the main trial in the R33 Phase. All participants will be recruited from the SH and CH in Lao PDR. All participants will undergo an informed consent process. Participants will be informed of the nature of the investigation, the steps that they will complete, and the types of interventions involved.

In the R21 Phase, the Lao research team will use purposive sampling to select potential participants (i.e., healthcare providers and patients) from the participating hospitals as described in the section D2 above. The Lao research team will directly contact potential participants and invite them to participate. The whole informed consent process and interviews or focus group discussions will be conducted in Lao by local research staff and will take place in a quiet, private location (e.g., an empty room) at the participating hospitals.

Specifically for the pilot and the main trial (R33 Phase), during the consent process, potential participants will be made aware that: (1) they are participating in a research study, (2) they will be asked to complete assessments according to research protocols, (3) they have a chance of being randomized to either the SC or AT arm of the study, and (4) their study data, without any identifiers, will be posted on the US ClinicalTrials.gov website. Participants will receive explanations about the potential risks of participation, measures to protect against risks, and the alternative option of not participating. In addition, research staff will explain how information related to study participation will be handled, including data management and plans to publish data in group format without identifying information. The whole informed consent process will be conducted in Lao by local research staff and will take place in a quiet, private location at the participating hospitals. Participants will be given up to one month to discuss the study participation with their families and to consider participating. Individuals wishing to enroll will be asked to sign an IRB-approved informed consent form.

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.
- To minimize the risk of participant information being disclosed via IDIs or FGDs in Phase 1, participants will be instructed to use initials to refer to themselves. Participants will also be advised not to use their names or mention another's name during discussions. Any names accidentally mentioned during group discussions will be replaced with the initial of the first name or with a random initial when transcribed.
- 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.
- In the pilot and main trials, 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.

In the pilot and main trials, 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

Hypothesis: At the 12-month follow-up, 7-day point prevalence biochemically confirmed abstinence (primary outcome) will be higher in the AT (vs. SC) group.

The primary abstinence analysis will be intention-to-treat; patients not completing follow-up assessments will be considered smokers. However, we will explore other ways of dealing with missing data (see below). Based on our previous work and assuming attenuation of abstinence rates across the follow-up visits, we anticipate that the 7-day point prevalence abstinence at the 12-month follow-up will be 8% in the SC group and 17% in the AT group. With 250 participants in each group and assuming a two-sided alpha of 0.05, we will have 86% power to detect a difference of 9% in 12-month 7-day point prevalence abstinence in the overall sample. It is unknown whether factors associated with smoking cessation differ by sex; it seems likely given the variation in smoking prevalence between sexes. Thus, we chose a sample size that gives 80% power to detect this difference in a subgroup analysis of only males (n=425, 85% of the sample). The sub-sample of females (n=75) gives 80% power to detect a 25% difference in 12-month 7-day point prevalence abstinence.

To estimate the effect of AT on abstinence rates while accounting for the potential clustering of participants recruited from the 2 clinic sites, we will use generalized linear mixed models (GLMM) analysis in which intervention groups (AT vs. SC) will be estimated as a fixed effect while the clinic will be modeled as a random effect nested within treatment condition. Sex can also be modeled as a random effect nested within clinic and treatment condition. Specifically, log binomial mixed models will be used to estimate the relative risk of quitting in the AT (vs. SC) group. Although groups should be similar in baseline characteristics due to randomization, we will explore models that control for any demographic or clinical variables that differ between treatment groups at baseline. We will also use GLMM models to examine changes in abstinence rates over time, while accounting for relevant baseline covariates. Similar

GLMM or linear mixed model (LMM) methodology, as appropriate for each outcome variable, will be used to examine other smoking-related variables, such as continuous abstinence, prolonged abstinence, and quit attempts. This project focuses on the latter 3 PBM phases, and thus we will explore phase-specific outcomes such as abstinence attainment and number of days smoking/abstinent. Statistical analyses will be performed using SAS 9.4 (SAS Institute, Inc.).

Potential treatment mechanisms will be examined via mediation analyses with intervention group (AT vs. SC) being the independent variable, abstinence at 12 months being the outcome variable, and the hypothesized mechanisms (motivation, self-efficacy, stress/negative affect) being potential mediators. The PROCESS macro for SPSS/SAS[103,104] will be used to identify variables (e.g., motivation, self-efficacy) that mediate the relationship between treatment condition and smoking cessation outcomes. This method uses an ordinary least squares path analytic framework to estimate direct and indirect effects in single and multiple mediation models, and bootstrapping methods are incorporated to generate confidence intervals.

Missing data and dropouts. Although treating participants lost to follow-up as smoking is a widely used strategy in smoking cessation studies, some researchers point to problems with this approach, especially when comparing treatment arms with differential dropout rates.[105] Thus, we will conduct sensitivity analyses to test for treatment differences assuming different missing data mechanisms. For example, we will consider a multiple imputation approach based on smoking-related patient characteristics at baseline, as well as demographics to account for potential missing-at-random mechanisms. We will also explore pattern-mixture and selection models to account for potential (and likely) missing-not-at-random mechanisms.[106] Similar findings based on these analyses will strengthen our study conclusions.

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.

Stages 1–4 of the R21 Phase have minimal risk. The research team will protect participants' privacy and confidentiality as described in section P below.

In Stage 5 (pilot trial) and R33 Phase (main trial), we will consult the Lao IRB to see if and how a Data Safety and Monitoring Board (DSMB) should be established. The DSMB will be responsible for monitoring rates of enrollment and for reviewing patient safety, risks of participation, protocol adherence by the research team, safety and confidentiality of data collection, data entry, and statistical issues. The DSMB may consist of five members, from both OUHSC and Lao institutions, who will oversee safety issues and overall conduct of the study. The DSMB will decide their meeting frequency for the specific purposes of data and safety monitoring. Relevant unanticipated problems, adverse events, or participants' concerns will be reviewed at these meetings. Summaries of all relevant discussions will be promptly disseminated to study personnel via e-mail, and retraining procedures will be implemented as needed. Appropriate modifications will be made in consultation with the OUHSC IRB and the designated program person at the NCI if necessary.

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 for Interviews and Focus Group Discussions (FGDs)

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.

- Online meeting option for FGDs: Research staff will set up a Zoom meeting for all FGDs. FGD participants will be given the option to participate online via Zoom. In-person attendance of FGDs will be limited to 10 persons, including research staff.
- Body temperature check: Before in-person interviews or FGDs, 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/FGD. Persons with a temperature >38.5^{o}C will not be allowed to participate in the interviews/FGDs 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/FGDs.
- Hand washing: Research staff and participants will be asked to wash their hands before and after the interviews/FGDs.
- 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.
- To minimize the risk of participant information being disclosed via IDIs or FGDs in Phase 1, participants will be instructed to use initials to refer to themselves. Participants will also be advised not to use their names or mention another's name during discussions. Any names accidentally mentioned during group discussions will be replaced with the initial of the first name or with a random initial when transcribed.
- 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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