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"Assessing the Efficacy of THR Products: A Randomized Controlled Trial in LMIC Populations"

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Abstract

As a result of increasing tobacco smoking, LMICs may account for a disproportionately high number of deaths caused by tobacco use worldwide. In order to deploy tobacco harm reduction (THR) products as an effective smoking cessation approach to limit escalating tobacco use in LMICs, it is vital to understand and perform RCTs in this setting. In this randomized controlled trial (RCT), 258 adult smokers will participate over the course of 52 weeks; each arm will get a 12-week treatment and a 12-week follow-up period. After participants fulfill the requirements and provide their informed permission, they will be randomly assigned to one of two treatment groups: (1) e-cigarettes with individual counseling and a nicotine patch dose of 21 mg or (2) nicotine patches with individual counseling and a nicotine concentration of 18 mg/ml. Both a screening and a baseline (BL) visit will be planned for participants at the trial location. A total of eight study visits, comprising five treatment sessions and three follow-up visits, will be arranged for the participants. These visits will include both in-person contacts at the trial site and telephone follow-up. In all, eight visits are scheduled for weeks 1, 2, 4, 8, 12, 18, 24, and 52. For the purpose of quantifying biochemically confirmed smoking abstinence, the trial site will use exhaled carbon monoxide evaluation.

Keywords: Smoking cessation, Tobacco harm reduction, E-cigarettes, Nicotine patches, LMIC

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INTRODUCTION

LMICs bear an inexplicably larger share of the burden of tobacco-related death globally due to rising tobacco consumption [1-3]. The weighted mean current smoking prevalence was 16.5% across 82 LMICs, with males being more likely to smoke than women. From 1.1% in Ghana to 50.6% in Kiribati, the prevalence of smoking tobacco differed across these nations [4]. In addition, 7.8 million people in lower-middle income nations and 2.1 million in low-income countries use e-cigarettes [5]. Tobacco smoking cessation programs should be prioritized by policymakers in order to lessen the impact of tobacco-related deaths and illnesses [6]. Additional research is needed to develop effective treatments for tobacco cessation due to the noticeable disparities in product usage and prevalence between high-income and low-income countries [1, 7]. The high rate of tobacco use in low and middle income countries has led to the adaptation of tobacco cessation programs from high-income nations to fit the local situation [8]. The efficacy of these studies is still debatable, nevertheless, because of cultural diversity and poor infrastructure in LMICs [9]. It is critical to

perform clinical studies in LMICs to aid smoking cessation because of the growing tobacco usage and the problems it causes.

There have been a lot of research on smoking cessation, including observational and quasi-experimental studies, in Low- and middle-income countries (LMICs) have few randomized controlled trials (RCTs) on the topic of tobacco cessation [1]. Of the 138 low- and middle-income countries (LMICs) included in the analysis, 92 randomized controlled trials (RCTs) on smoking cessation were found in 16 of those countries. The countries with the highest number of trials were Thailand (9.1%), India (26.2%), and China (17.8%). Psychosocial (n = 52, 57%), psychosocial/behavioral (n = 20, 21%), pharmacological/behavioral (n = 9, 10%), pharmacological (n = 8, 9%), and behavioral (n = 3, 3%), were the various intervention categories used in these total RCTs. More than two-thirds of the programs specifically targeted non-brand smokers. Pakistan was the site of six research, the most majority of which used psychosocial/pharmacological therapies (83%). Evidence quality was found to be weak in China compared to high-income nations, with the exception of psychosocial RCTs. RCTs were little compared to the huge cigarette death toll in the area [1], which affects all LMICs. Some of the primary obstacles to conducting tobacco cessation RCTs in LMICs include tobacco industry activities [10], patients' apparent unwillingness to quit smoking [11], a lack of knowledge about pharmacological therapies [12], and inefficient government policies [13]. In addition, there was a lack of emphasis on behavioral and pharmaceutical options in the randomised controlled trials (RCTs) pertaining to tobacco cessation in low- and middle-income countries (LMICs). According to the review's findings, even though there is some evidence from randomized controlled trials (RCTs) in low- and middle-income countries (LMICs), these countries are still not seen as having established best practices for tobacco cessation. As a result, effective tobacco control in LMICs requires local solutions that are tailored to their specific context [1]. While there have been some randomized controlled trials (RCTs) in low- and middle-income countries (LMICs) that have looked at the effectiveness of tobacco harm reduction (THR) products like e-cigarettes and nicotine replacement therapies (NRTs), the results have been inconclusive because the trials were either pilot studies or only included male smokers. This shows that more RCTs are needed to determine whether THR products are effective. The majority of the randomized controlled trials (RCTs) performed in low- and middle-income countries (LMICs) included nicotine patches, with only one research including electronic cigarettes and Korean male smokers. Clinical trials continue to be the gold standard for evaluating interventions, despite the problems associated with randomised controlled trials (RCTs), such as results being overgeneralized, limited sample sizes, validity, and reliability [17]. Research trials focusing on helping people quit smoking seem to be the gold standard for assessing the efficacy of tobacco control initiatives [18]. Using THR products as a smoking cessation approach to curb escalating tobacco use in LMICs requires understanding and performing RCTs in context to LMICs, considering the aforementioned shortcomings found by numerous research in LMICs. So yet, no randomized controlled trial (RCT) has been conducted to compare the efficacy of various THR products in adults in low- and middle-income countries.

MATERIALS AND METHODS

Study Design

The trial is a two-arm, parallel randomized controlled trial with a 12 weeks treatment duration and long-term 52 weeks follow-up. A schematic diagram of the trial design is given in **Figure 1**.

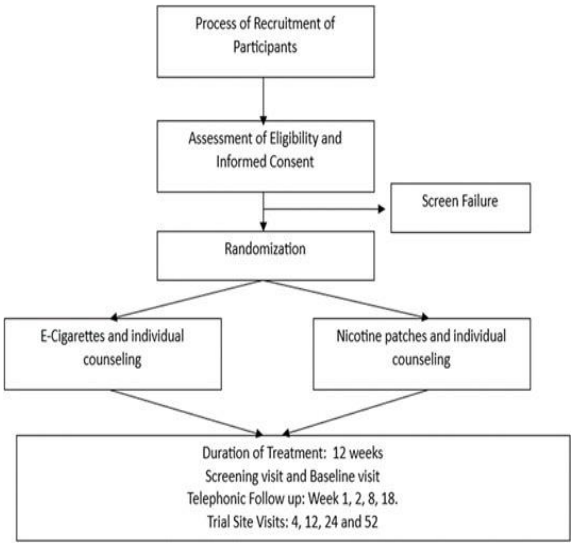

Figure 1. Schematic Diagram of Trial Design

Primary and Secondary Outcomes

The primary outcome measures for the study will be:

• Commonality The number of individuals who self-reported not using any substances in the last seven days, with the biochemical verification that their exhaled carbon monoxide levels were less than or equal to 10 parts per million.

When you come in for your stop date, therapy, and follow-up appointments, we'll check for the following secondary outcomes:
• Point Prevalence after seven days: The total number of people who said they didn't light up in the last week

• Cigarette Use: Participants recorded their daily cigarette smoking in their diaries.
• How Others See the Product: Participants' opinions on electronic cigarette and patch usage as measured by a modified cigarette assessment form. To measure how people feel about the product, we asked them twelve questions. The score may be anywhere from -6 to +6, with higher positive values indicating that a higher dosage has a stronger impact.
To assess the likelihood of adverse events related to nicotine patches and EC, the Naranjo Adverse Drug Reaction Probability Scale will be used. Higher numbers indicate certain unfavorable medication effects, and the overall scores may range from -4 to +13.
• Dependence and Withdrawal Symptoms: To evaluate dependence and withdrawal symptoms, the Fagerstrom test for nicotine will be administered. It evaluates smoking frequency, dependency, and use quantity via six different components. A final score is generated by adding together all of the things. from zero to ten. A higher score suggests that nicotine has a strong bodily impact on the user.

Dissemination and Ethics

All procedures related to the conduct of the research will adhere to the following: the Declaration of Helsinki, the Good Pharmacoepidemiology Practices Guidelines, the International Conference on Harmonization's Good Clinical Practice Guidelines, and any regulations that may be relevant to randomized controlled trials. All participants were asked to provide their informed permission before the trial began.

Subjects Under Investigation

We will include adults in the research who use tobacco cigarettes and are motivated to stop from the general population in LMICs.

Eligibility Requirements for Participation

In order to be eligible to participate in the study, individuals must meet the following criteria: be of legal smoking age according to the country's laws; smoke only combustible cigarettes; have an exhaled carbon monoxide level greater than ten parts per million; desire to quit smoking; possess a mobile phone; be able to comply with all study procedures; and be available for follow-up. However, this medication will not be sold to pregnant or nursing women, anybody taking any other nicotine replacement therapy (NRT), anyone participating in a smoking cessation program or randomized controlled trial (RCT), and anyone with a history of cardiovascular disease or other serious illness for whom the prognosis is shorter than one year.

Recruiting and Scheduling

The trial site may be contacted by phone, email, or the study website; volunteers will be recruited via outpatient clinics and marketing. Permission from respondents is required for two phases in the consent process: screening and randomization. Participants are invited to the trial location for the zero visit, which consists of screening and signing a permission form, if they agree. Within two months of starting the experiment, the site will have recruited and identified all participants. the very first hiring. As part of the screening process, the research coordinator will verify each response against the inclusion criteria checklist. Subsequently, we will collect baseline data and then randomly assign eligible participants to one of the two research arms, with research Arm A consisting of nicotine e-cigarettes and Study Arm B consisting of nicotine patches, at a ratio of 1:1. The lead investigator will utilize a web-based tool to produce a random sequence.

Medical Protocols

Study Arm A participants will get an EC device supply and nicotine cartridges (18 mg/ml) to last until their next in-person appointment. It is recommended that individuals familiarize themselves with ad libitum usage one week before to their stop date. On the quit day,

participants will transition to using e-cigarettes for the subsequent twelve weeks. The majority of the studies used the 18 mg EC level, which is deemed an acceptable alternative for smokers who consume ten cigarettes or more per day [15]. In contrast, those assigned to the B group will get a supply of nicotine patches (21 mg) to last them until their next scheduled in-person appointment. The participants will put down the cigarette and start using the nicotine patch every day for 12 weeks on their designated quit day. Based on the results of the studies, the nicotine patch strength of 21 mg is a good alternative for those who smoke 10 cigarettes or more each day [19-22].

Investigational Sites and Methods

The study location will arrange screening and baseline (BL) visits for participants. Through a mixed-mode approach that incorporates both in-person and telephone interactions with the respondents, a total of eight research visits—five treatment sessions and three follow-up visits—are planned for the participants. At1,2,4,8,12,18,24, and 52 weeks into the research, you will have eight planned appointments. In Table 1 you can see the study visit schedule in great detail.

Table 1. Study Visit Schedule

Visit	Window	Visit Type	CRF	Questionnaires	Physical Measures	Counseling
Baseline	N/A	At Site	Yes	• Fagerstrom questionnaire • SCQoL • mCEQ • BDI-II	• eCO breath test • BMI • Vital signs	30 minutes
1st Week	±2 days	Telephone	Yes	N/A	N/A	10 minutes
2nd Week	±2 days	Telephone	Yes	N/A	N/A	10 minutes
4th Week	±7 days	At Site	Yes	• Fagerstrom questionnaire • SCQoL • mCEQ • BDI-II	• eCO breath test • BMI • Vital signs	20 minutes
8th Week	±2 days	Telephone	Yes	N/A	N/A	10 minutes

12th Week	±7 days	At Site	Yes	• Fagerstrom questionnaire • SCQoL • mCEQ • BDI-II	• eCO breath test • BMI • Vital signs	15 minutes
18th Week	±2 days	Telephone	Yes	N/A	N/A	10 minutes
24th Week	±7 days	At Site	Yes	• Fagerstrom questionnaire • SCQoL • mCEQ • BDI-II	• eCO breath test • BMI • Vital signs	15 minutes
52nd Week	±7 days	At Site	Yes	• Fagerstrom questionnaire • SCQoL • mCEQ • BDI-II	• eCO breath test • BMI • Vital signs	15 minutes

Loss to Follow Up

In comparison to other types of clinical trials, loss to follow- up in studies on quitting is often higher, with losses of 20– 30% or more being common [23].

Safety Data Collection

Study staff will gather data on adverse events (AEs) at every follow-up appointment. It will be advised that participants who experience any adverse events (AEs) that might be linked to the investigational product contact the study team immediately if their symptoms worsen or change. Over the course of the follow-up period, the trial team will keep an eye out for adverse events. The PI will use the Naranjo Scale to assess and categorize all SAEs. The trial site's Data and Safety Monitoring Committee (DSMC) will keep an eye on any reports of serious adverse drug responses. In order to guarantee the safety of the trial participants, DSMC will establish an impartial stopping criteria based on the products' safety profiles.

Sample Size Calculation

Twenty percent of smokers who used EC [24–27] reported a CO-validated decrease in smoking after six months, but just seven percent of smokers who used NRT [28] did the same. Research on smoking cessation also has a greater loss to follow-up rate than other clinical trial categories, with rates of 20-30% or more being reported often [23], Our power analysis is predicated on previous studies that found an 11% disparity between the two groups, with 20% reporting smoking cessation in the e-cigarette group and 7% in the NRT group. With a two-sided significance level of 0.05, beta = 0.2, and a 95% confidence interval, a sample size of 107 responses is needed for each group to obtain 80% power. According to the literature, a sample size of 258 was needed, with 129 responders in each arm, after accounting for a 20% dropout rate.

Data Analysis

By regressing smoking status in each study arm, we will analyze the main and secondary outcomes of smoking cessation, reduction, and abstinence at each time point in the trial group. Using binomial regression, we will calculate the relative risk for both research groups. Primary analyses will be conducted to take the stratification factor into consideration.

modified to account for the location of the experiment, and baseline variables chosen by stepwise regression to conduct sensitivity analyses will also be modified. The mean differences between the two groups will be estimated at 95% confidence intervals using a generalized linear model with binary regressions. The variables that will be measured include product ratings, change scores for withdrawal symptoms at baseline and follow-up, and the number of participants who experienced adverse reactions. Furthermore, in order to analyze the main consequence, comprehensive case studies will be carried out. We will investigate time-to-relapse using Kaplan Meier curves, the log-rank test, and Cox proportional hazards regression analysis; for effect consistency for pre-specified subgroups based on demographic variables, we will employ test of heterogeneity.

RESULTS AND DISCUSSION

Both clinical decision-making about the use of THR products for smoking cessation and the improvement of smoking abstinence among smokers in LMICs will be aided by the findings of this clinical investigation. We have identified a few issues with the research design. An important issue is the selection of intervention items. Despite the proliferation of electronic cigarette devices, very little is known about their safety or efficacy [29]. The effectiveness and acceptability of a particular e-cigarette model could affect the results obtained from studies. The trial will employ 21mg nicotine patches as they are the most regularly used product among NRTs. If you're worried that electronic cigarettes are causing any health problems, a patch may help you figure it out. People who use e-cigarettes say it takes a while to become used to them before they're pleased, and studies have shown that only new

users experience high nicotine levels [30]. We gave participants detailed, illustrated instructions on how to use e-cigarettes and had them try them out for a week before they started trying to stop smoking in an effort to remedy this. Efficacy and safety will be reported throughout the trial's 12-week monitoring period. Twelve weeks should provide enough time to evaluate any unanticipated side effects. With these results, the Cochrane Systematic Review on e-cigarettes for reducing and quitting smoking will be much more comprehensive [31].

CONCLUSION

The purpose of this randomized controlled study is to determine if tobacco harm reduction products are safe and effective for adults in low- and middle-income countries. We expect this study's findings to add to and strengthen the body of evidence supporting e-cigarettes as a tool for smoking cessation.

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