Original Article

Protocol for Randomized, Two Arm Parallel, Clinical Trial for Effectiveness of THR Products in LMIC

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Abstract

LMICs bear an inexplicably larger share of the burden of tobacco-related death globally due to rising tobacco consumption. Understanding and conducting RCTs in the context of LMICs is mandatory to use THR products as an effective smoking cessation strategy for controlling rising tobacco consumption in these countries. The study is a two-arm, parallel RCT with a 12-week treatment period and a 52-week follow-up period which plans to enroll 258 smokers from general adult population. The participants after meeting eligibility criteria and providing informed consent will be randomized (1:1) to one of two treatment arms: (1) E-cigarettes (18mg/ml) with individual counseling (2) Nicotine patches (21mg) with individual counseling. Participants will be scheduled for a screening visit and a baseline (BL) visit at the trial site. The participants will be scheduled for eight study visits in total, including five treatment sessions and three follow-up visits, using both face-to-face interactions at the trial site as well as follow-up on the telephone. Eight study visits are planned at weeks 1, 2, 4, 8, 12, 18, 24, and 52. Exhaled carbon monoxide assessment will be used at the trial site to quantify biochemically validated smoking abstinence.

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

Introduction

LMICs bear an inexplicably larger share of the burden of tobacco-related death globally due to rising tobacco consumption [1-3]. A survey conducted in 82 LMICs highlighted that the weighted mean current smoking prevalence was 16.5% which was seen as higher among men as compared to women. The prevalence of smoking tobacco varied among these countries ranging from 1.1% in Ghana to 50.6% in Kiribati [4]. Moreover, approximately 2.1 million users of e-cigarettes reside in low-income countries and 7.8 million in lower-middle-income countries [5]. To reduce the consequences of tobacco-related morbidity and mortality, policymakers should give prime importance to tobacco smoking cessation interventions [6]. Major differences in the prevalence and products use among high and low-income countries have been witnessed which require further research for identifying effective tobacco cessation strategies [1, 7]. Due to the high prevalence of tobacco use, LMICs are adapting successful tobacco cessation interventions from high-income nations for replication according to their local context [8]. However, due to diverse cultures and inadequate infrastructure in LMICs, the effectiveness of these investigations is still unclear [9]. Due to the rising incidence of tobacco use in LMICs and its associated challenges, it is necessary to support smoking cessation by conducting clinical trials in these countries.

Although many studies such as observational and quasi-experimental, have been conducted on quitting smoking in LMICs, limited tobacco cessation randomized controlled trials (RCTs) are found in these countries [1]. A comprehensive scoping review highlighted ninety-two tobacco cessation RCTs conducted in 16 of 138 LMICs countries including India (n = 26, 28 %), China (n = 17, 18%), Thailand (n = 9, 10%) followed by other nations (n = 40, 44 %). Of these total RCTs, different types of intervention used were: psychosocial (n = 52, 57 %), psychosocial/ behavioral (n = 20, 21%), pharmacological/ behavioral (n = 9, 10%), pharmacological (n = 8, 9%) and behavioral (n =3, 3%). Moreover, 65 % of the interventions targeted generic smokers. Six studies were conducted in Pakistan with 83% being psychosocial/pharmacological and 17 % psychosocial interventions. It was observed that except for psychosocial RCTs in China, the quality of evidence was largely not strong as compared to high-income countries, and RCTs were

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limited across all LMICs, in comparison to the large tobacco mortality burden in the region [1]. Activities by the tobacco industry [10], apparent patient reluctance to tobacco cessation [11], inadequate awareness regarding pharmacological treatments [12], and ineffective government policy [13] were found as the main factors hindering the conduction of tobacco cessation RCTs in LMICs. Moreover, the conducted RCTs around LMIC tobacco cessation were found inclined towards psychosocial interventions with limited focus on behavioral and pharmacological alternatives. The findings of the review also highlighted that despite the availability of weak evidence for RCTs conducted in LMICs, tobacco cessation in these countries is still not considered a setting where best practice has been established, therefore, specific solutions befitting the local context of LMICs is vital for effective tobacco control in these countries [1]. Although, few RCTs conducted in LMICs were found which evaluated the efficacy of THR products including NRT and e-cigarettes [14] but their findings were not conclusive as either it was a pilot trial [15] or focused on only male smokers [14] and the results could not be generalizable to other populations highlighting the need of conduction of more RCTs on assessment of the efficacy of Tobacco Harm Reduction (THR) products including e-cigarettes as well as other NRTs. The RCTs conducted in LMICs indicate that most of the studies were conducted using nicotine patches while only a single study was found on Korean male smokers using e-cigarettes. Despite of the inherent issues linked with RCTs including the overgeneralization of result, small samples [16], validity, and reliability [17], clinical trials are still the most reliable approach to evaluate an intervention. Tobacco cessation RCTs seem to be the most effective clinical studies to evaluate tobacco control activities [18]. Taking into account the above gaps identified by various studies conducted in LMICs, understanding and conducting RCTs in context to LMICs is mandatory in order to use THR products as an effective smoking cessation strategy for controlling rising tobacco consumption in these countries. Hence, this is the first RCT that has been designed to evaluate the effectiveness of different THR products in the general adult population in LMIC.

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**.

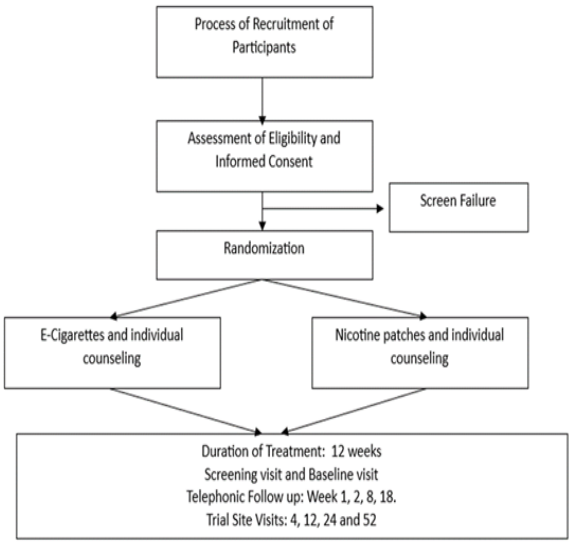

Figure 1. Schematic Diagram of Trial Design

Primary and Secondary Outcomes

The primary outcome measures for the study will be:

- *Point Prevalence Abstinence:* The number of participants self-reported abstinence in the past week, with biochemical validation using exhaled carbon monoxide ≤10 parts per million.

The below-mentioned secondary outcomes will be assessed on the day of quitting, treatment, and follow-up visits:

- *Seven-day Point Prevalence:* Number of participants self-reporting for not smoking cigarettes during the last 7 days
- *Use of Combustible Cigarettes:* The number of cigarettes smoked per day was assessed using self-reported diaries
- *Perceptions Regarding the Product:* Views of participants on the use of EC or patches using a modified cigarette evaluation questionnaire. Twelve questions are used to quantify perceptions of the product. The score can range from -6 to +6; increasing positive scores refer to a high dose producing an effect with greater intensity.
- *Adverse Events:* The Naranjo Adverse Drug Reaction Probability Scale will be used to analyze adverse events associated with nicotine patches and EC. Overall scores can vary from -4 to +13, with higher values indicating definite adverse drug reactions.
- *Withdrawal Signs and Symptoms and Dependence:* Fagerstrom test for nicotine dependence will be used to assess signs and symptoms of withdrawal and dependence. It has six components that assess smoking frequency, dependence, and amount of use. The items are added up to produce a final score

between 0 and 10. A higher score indicates severe physical dependence on nicotine.

Ethics and Dissemination

The Declaration of Helsinki, the Good Clinical Practice Guidelines of the International Conference on Harmonization, Good Pharmacoepidemiology Practices Guidelines, and/or any applicable laws governing RCTs will be followed in the conduct of the study. Before the start of the study, informed consent was collected from all the respondents.

Study Population

Adults who smoke tobacco cigarettes among the general population in LMICs and have the motivation to quit will be included in the study.

Inclusion and Exclusion Criteria

Both genders of the legal age allowed for smoking as per country law, regular smokers of only combustible cigarettes (smoked at least ten cigarettes a day for the past year), exhaled breath eCO level > ten ppm, wish to quit smoking, having a mobile phone, able to conform with all study procedures and expected to be available for follow up will be enrolled as study participants. However, pregnant or nursing women, anyone taking any other NRT and/or enrolled in any other smoking cessation program/RCT, having any contraindications to products such as cardiovascular history and/or suffering from a major illness with a prognosis of less than 1 year will be excluded.

Recruitment and Randomization

Outpatient clinics and advertisements will be used for the recruitment of participants and directed to contact the trial site by phone, email, or through the study website. The process of consent will include two steps involving permission from respondents for (1) screening and (2) randomization. If the participant agrees he/she will be invited to the trial site for the zero visit i.e., screening and signing a consent form. The trial site will complete the process of identification and recruitment of all study participants within two months from the first recruitment. The respondents will be verified by the study coordinator according to the inclusion criteria checklist and will be screened. After this, baseline information will be gathered and eligible respondents who agree to participate will be randomly assigned (1:1) to one of the study arms i.e. Study Arm A: Nicotine E-Cigarettes and Study Arm B: Nicotine patches. A web-based application will be used to issue a computer-generated sequence for randomization by the principal investigator.

Treatment Regimens

Participants randomized to Study Arm A will be provided nicotine cartridges (18 mg/ml) and EC devices supply to last till the next in-person visit. One week before their designated quit date, ad libitum use will be advised to the participants to become familiar and on the quit date participants will switch to using e-cigarettes for the next twelve weeks. The 18 mg EC strength is considered an adequate substitute for smokers who smoke at least ten cigarettes/per day and is used in most of the trials [15].

On the other hand, participants randomized to study arm B will be provided a 21 mg nicotine patches supply to last till the next in-person visit. On their allocated quit day, the participants will stop smoking and use one nicotine patch daily for the next twelve weeks. The 21 mg nicotine patch strength is considered a suitable substitute for smokers who smoke at least ten cigarettes/day and is used in most of the trials [19-22].

Study Visits and Procedures

Participants will be scheduled for a screening visit as well as a baseline (BL) visit at the trial site. The participants will be scheduled for eight study visits in total, including five treatment sessions and three follow-up visits, using a mixed-mode method that includes interaction with the respondents through telephone calls as well as face-to-face at the trial site. The eight study visits will be scheduled at weeks 1, 2, 4, 8, 12, 18, 24, and 52. A detailed description of the schedule of study visits is given in **Table 1**.

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

At all follow-up visits, information regarding AEs will be collected by study personnel. respondents who suffer adverse events (AEs) that may be connected to the investigational product will be instructed to get in touch with research staff if their symptoms change or get worse. During the follow-up duration, AEs will be monitored by the trial team. All SAEs will be evaluated and classified using the Naranjo Scale by the PI. A Data and Safety Monitoring Committee of the Trial Site (DSMC) will monitor all reports of Serious adverse drug reactions. According to the safety profile of the products, DSMC will develop an independent stopping criterion for the trial to ensure the safety of the participants.

Sample Size Calculation

The literature reveals 20% of the smokers using EC [24-27] achieved CO-validated smoking reduction at 6 months as compared to 7% of those using NRT [28]. Moreover, in comparison to other types of clinical trials, higher loss to follow-up in studies on quitting smoking is reported, with losses of 20-30% or more being common [23], Our power calculation is based on earlier research, where 20 % reported smoking abstinence in the e-cigarette group and 7 % in the NRT group, i.e., an 11 % difference between the two groups. To achieve 80% power with a significance level of 0.05 (two-sided), beta = 0.2, and 95 % confidence interval, a sample size of 107 respondents is required in each group. Based on literature 20% dropout was considered, adding 22 participants in each group making the total sample size of 129 respondents in each arm with a total required sample size of 258.

Data Analysis

Analysis of cessation and reduction of smoking along with abstinence in primary and secondary outcomes at each time point in the trial group will be done by regressing smoking status in each study arm. Calculation of relative risk for both study groups will be performed using binomial regression. To account for the stratification factor, primary analyses will be adjusted for the trial site while baseline covariates selected with the use of stepwise regression for sensitivity analysis will also be adjusted. A generalized linear model using binary regressions for estimation of mean differences at 95% confidence intervals between both groups in terms of product ratings, change scores for withdrawal symptoms at baseline and follow-up, and the number of participants experiencing adverse reactions will be conducted. Additionally, complete case analyses will be conducted for analysis of the primary outcome. Test of heterogeneity will be used for assessing the consistency of effects for pre-specified subgroups based on demographic characteristics, while Kaplan Meier curves, the log-rank test, and Cox proportional hazards regression analysis will be used to analyze time-to-relapse.

Results and Discussion

The results of this clinical trial will be used to enhance smoking abstinence among smokers in LMICs as well as clinical decision-making about the use of THR products for smoking cessation. A few challenges have been observed with the study design. The choice of intervention products is a crucial problem. There are many different types of e-cigarette products on the market, and their variety is rising, but there is little data on their effectiveness and quality [29]. Different findings may be collected from trials due to the efficacy and acceptability of a specific e-cigarette model. The most commonly used product is the nicotine patch among NRTs, therefore the study will utilize 21mg nicotine patches. The use of a patch will determine whether any adverse effect is due to e-cigarettes.

Users claim that they require some time to become comfortable with e-cigarettes before they feel satisfied, and tests that revealed only novice users had high nicotine levels due to e-cigarette usage [30]. We made attempts to address this by giving participants comprehensive, illustrated instructions on how to use e-cigarettes and mandating that they test them out for a week before starting their quit attempt. Throughout 12 weeks of monitoring, the trial will report on efficacy and safety. To assess any unreported adverse effects twelve weeks is sufficient. The findings will be an important addition to the Cochrane Systematic Review on electronic cigarettes for smoking cessation and reduction [31].

Conclusion

This randomized controlled trial will assess the effectiveness and safety of tobacco harm reduction products in the general adult population in LMICs. The results of this study are anticipated to strengthen and enrich the existing research that supports the smoking cessation use of e-cigarettes.

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