Society of Medical Education & Research

2023, Volume 3, Page No: 55-61
ISSN: 3108-4818

International Journal of Social and Psychological Aspects of Healthcare

Randomized Two-Arm Parallel Clinical Trial Protocol Assessing THR Product Effectiveness in LMICs

Madeeha Malik[1]*, Azhar Hussain[2], Ayisha Hashmi[1], Waleed Khan[1]

[1]Cyntax Health Projects PVT LTD, Contract Research Organization, Islamabad, Pakistan.
[2]Department of Pharmacy and Allied Sciences, Pak Austria Fachhochschule, Haripur, Pakistan.

***E-mail** ✉ madeehamalik19@gmail.com

Abstract

Tobacco-related mortality is disproportionately high in LMICs due to increasing consumption, making it essential to explore effective smoking cessation strategies. This study uses a randomized, two-arm parallel design to evaluate the role of THR products, including a 12-week intervention and a follow-up lasting 52 weeks. A total of 258 adult smokers will be recruited and randomly assigned in equal proportions to one of two intervention groups: (1) e-cigarettes (18 mg/ml) with individualized counseling or (2) nicotine patches (21 mg) with individualized counseling. Participants will undergo screening and baseline assessments at the trial site, followed by a total of eight study sessions scheduled over a year at weeks 1, 2, 4, 8, 12, 18, 24, and 52. The trial incorporates in-person and telephone-based follow-ups, with smoking abstinence confirmed by biochemical validation using exhaled carbon monoxide analysis.

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

Introduction

LMICs continue to experience a disproportionately high burden of tobacco-related mortality due to increasing tobacco consumption [1-3]. A study conducted across 82 LMICs reported that the overall weighted mean prevalence of current smoking was 16.5%, with higher rates observed among men than women. Smoking prevalence varied significantly among these nations, ranging from 1.1% in Ghana to 50.6% in Kiribati [4]. Additionally, an estimated 2.1 million e-cigarette users reside in low-income countries, while 7.8 million are found in lower-middle-income countries [5]. Given the serious health risks associated with tobacco use, prioritizing smoking cessation strategies should be a key focus for policymakers [6]. Substantial disparities exist between high- and low-income countries regarding tobacco consumption patterns and product usage, emphasizing the need for further studies to develop effective cessation interventions [1, 7]. In response to widespread tobacco use, many LMICs are working to implement successful cessation strategies originally developed in high-income countries, adapting them to local conditions [8]. However, due to cultural differences and limited healthcare infrastructure, the success of these approaches remains uncertain [9]. Considering the increasing tobacco use and its related health concerns in LMICs, conducting clinical trials in these regions is essential to support smoking cessation efforts.

Despite numerous observational and quasi-experimental studies on smoking cessation in LMICs, randomized controlled trials (RCTs) remain scarce in these regions [1]. A scoping review identified 92 tobacco cessation RCTs conducted in only 16 out of 138 LMICs, with the highest numbers reported in India (n = 26, 28%), China (n = 17, 18%), and Thailand (n = 9, 10%), while the remaining 40 trials (44%) were spread across other nations. These trials employed different intervention methods, including psychosocial approaches (n = 52,

Access this article online https://smerpub.com/

Received: 27 September 2023; **Accepted:** 05 December 2023

How to cite this article: Malik M, Hussain A, Hashmi A, Khan W. Randomized Two-Arm Parallel Clinical Trial Protocol Assessing THR Product Effectiveness in LMICs. Int J Soc Psychol Asp Healthc. 2023;3:55-61. https://doi.org/10.51847/k7feFG828H

57%), psychosocial combined with behavioral strategies (n = 20, 21%), pharmacological integrated with behavioral methods (n = 9, 10%), pharmacological-only interventions (n = 8, 9%), and behavioral strategies alone (n = 3, 3%). Additionally, 65% of these interventions targeted the general smoking population. In Pakistan, six trials were conducted, of which 83% used psychosocial and pharmacological approaches, while 17% relied solely on psychosocial methods. Except for psychosocial RCTs in China, the overall quality of evidence was relatively weak compared to high-income countries, and the number of RCTs remained inadequate given the high tobacco-related mortality in LMICs [1].

Multiple barriers have limited the implementation of tobacco cessation RCTs in these countries, including industry interference [10], unwillingness among smokers to quit [11], lack of awareness regarding pharmacological treatments [12], and ineffective policy measures [13]. Furthermore, research in LMICs has primarily centered on psychosocial interventions, with minimal focus on behavioral and pharmacological alternatives. Given the weak evidence base for RCTs in these regions, tobacco cessation strategies have yet to be standardized as best practice, underscoring the importance of developing context-specific solutions to strengthen tobacco control efforts [1].

Limited RCTs have assessed the efficacy of THR products, such as nicotine replacement therapy (NRT) and e-cigarettes, in LMICs [14]. However, findings from these studies remain inconclusive due to constraints such as pilot trial designs [15] and an exclusive focus on male smokers [14], limiting their applicability to broader populations. The available data indicate that most RCTs in LMICs have investigated nicotine patches, with only one study examining e-cigarette use among Korean male smokers. While challenges such as small sample sizes [16], issues of generalizability, and concerns about validity and reliability [17] persist, RCTs remain the gold standard for evaluating intervention effectiveness. Tobacco cessation RCTs provide the most reliable framework for assessing control strategies [18]. Given the research gaps in LMICs, clinical trials are crucial to determine the role of THR products in smoking cessation. This study is the first RCT designed to evaluate the effectiveness of various THR products among the general adult population in LMICs.

Materials and Methods

Study design

This study follows a two-arm, parallel design as a randomized controlled trial, incorporating a 12-week treatment phase along with an extended 52-week follow-up period. The trial structure is visually represented in **Figure 1**.

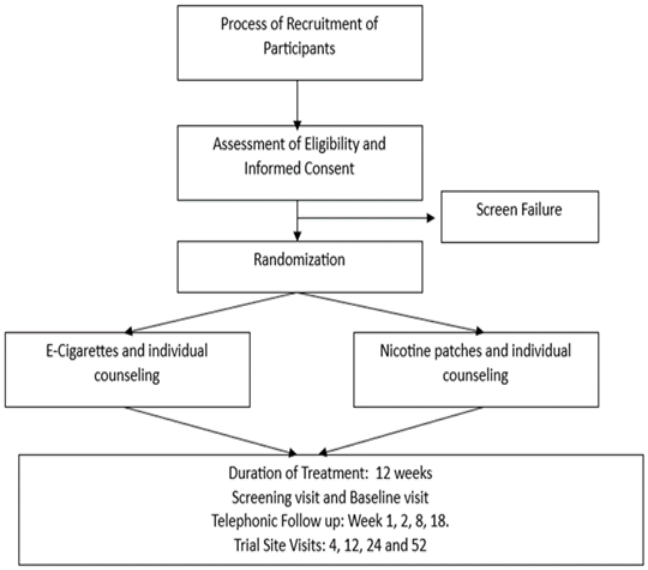

Figure 1. Schematic diagram of trial design

Primary and secondary outcomes

The study's primary outcome will be:

- Point prevalence abstinence: The proportion of participants who report not smoking in the past week, with biochemical verification through exhaled carbon monoxide levels of ≤ 10 parts per million.

Secondary outcomes will be assessed at the quit date, during treatment, and at follow-up visits:

- Seven-day point prevalence: The number of participants who report no cigarette use in the last seven days.
- Cigarette consumption: Daily smoking frequency recorded through self-reported diaries.
- Product perception: Participant opinions on EC or nicotine patches, were evaluated using a modified cigarette assessment tool consisting of twelve questions. Scores range from -6 to +6, with higher values indicating a stronger perceived effect.
- Adverse reactions: The Naranjo adverse drug reaction probability scale will be applied to assess side effects associated with nicotine patches and EC use. Scores range from -4 to +13, where higher values indicate a confirmed adverse reaction.
- Withdrawal and dependence: The Fagerstrom test for nicotine dependence will measure withdrawal symptoms and dependence levels. This test consists of six questions assessing smoking frequency and nicotine reliance, producing a total score from 0 to 10, with higher values indicating greater dependence.

Ethical standards and dissemination

This study will adhere to ethical principles outlined in the Declaration of Helsinki, as well as the International Conference on Harmonization's Good Clinical Practice guidelines, Good Pharmacoepidemiology Practices, and relevant local laws for RCTs. Informed consent will be obtained from all participants before initiating the study.

Population for the study

The study will target adult smokers from the general population in LMICs who have expressed a desire to quit smoking.

Eligibility criteria

Participants must be adults of legal smoking age as per local regulations, regular smokers who have consumed at least ten cigarettes a day for the past year, with exhaled CO levels greater than 10 ppm, and own a mobile phone. They should be willing to follow study protocols and be available for follow-up visits. Exclusion criteria include pregnant or breastfeeding women, individuals already using other nicotine replacement products or enrolled in another smoking cessation trial, and those with contraindications such as significant cardiovascular issues or life-limiting illnesses.

Recruitment and randomization process

Participants will be recruited through outpatient clinics and advertisements, with further details on contacting the trial site provided via phone, email, or the study website. The consent procedure will consist of two stages: first for screening, and second for randomization. Upon agreeing to participate, individuals will visit the trial site to complete the screening process and sign the informed consent form. Recruitment will be completed within two months of initiating participant enrollment. Eligibility will be checked by the study coordinator based on inclusion criteria, and once confirmed, baseline data will be collected. Participants who meet all criteria will be randomly assigned to one of the two treatment arms (1:1 ratio) using a computer-generated randomization system controlled by the principal investigator.

Treatment assignment

For Study Arm A, participants will receive nicotine e-cigarettes (18 mg/ml) with sufficient cartridges for use until their next visit. They will be instructed to use the e-cigarettes freely for one week before their designated quit date to familiarize themselves with the product, after which they will continue to use for the following 12 weeks. The 18 mg/ml strength is considered effective for individuals smoking at least ten cigarettes daily and has been used in various trials [15].

In Study Arm B, participants will receive 21 mg nicotine patches, which they will use daily for the subsequent 12 weeks. On their quit date, participants will stop smoking and begin using one nicotine patch each day. This nicotine patch dosage is appropriate for smokers who consume at least ten cigarettes daily and is widely utilized in clinical trials [19-22].

Study visits and protocols

Participants will undergo an initial screening visit followed by a baseline (BL) visit at the trial location. A total of eight study visits are planned, which include five

treatment appointments and three follow-up check-ins. These visits will utilize both in-person meetings at the trial site and remote follow-ups via telephone. The visits are scheduled for weeks 1, 2, 4, 8, 12, 18, 24, and 52. A comprehensive timeline for these visits is provided 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

Participant retention is often more challenging in smoking cessation studies, with dropout rates commonly ranging from 20% to 30% or higher compared to other types of clinical trials [23].

Safety monitoring

Adverse events (AEs) will be tracked during follow-up visits by the research team. Participants experiencing any AEs potentially linked to the study product will be advised to reach out to the study staff if their symptoms change or worsen. The trial team will monitor these events over the follow-up period. Serious adverse events (SAEs) will undergo evaluation and classification using the Naranjo Scale by the principal investigator (PI). Additionally, a Data and Safety Monitoring Committee (DSMC) will be established to oversee any reports of serious adverse drug reactions, and the DSMC will determine independent trial cessation criteria based on safety concerns for the participants.

Sample size calculation

Prior studies have shown that 20% of smokers using e-cigarettes achieved smoking reduction validated by CO at 6 months, compared to just 7% for those using nicotine replacement therapy (NRT) [24-28]. Smoking cessation trials generally face higher dropout rates, ranging from 20% to 30% [23]. For this trial, to detect an 11% difference in smoking abstinence between the e-cigarette and NRT groups (20% vs. 7%), a total of 107 participants per group is required to achieve 80 percent power, assuming a significance level of 0.05 (two-sided), β = 0.2, and a 95% confidence interval. Taking into account a 20% dropout rate, an additional 22 participants per group will be added, resulting in a final required sample size of 258 participants (129 in each group).

Data analysis

Primary and secondary results, including smoking cessation and reduction, will be analyzed at each study visit using regression models to assess smoking status in each group. Binomial regression will calculate the relative risk between the study groups. The primary analysis will control for the trial site as a stratification factor, and baseline covariates will be adjusted using stepwise regression for sensitivity analysis. A generalized linear model will estimate mean differences and 95% confidence intervals for product evaluations, changes in withdrawal symptoms, and the frequency of adverse events. A complete case analysis will be used for the primary outcome. Tests for heterogeneity will examine the consistency of effects within predefined demographic subgroups. Time-to-relapse data will be analyzed using Kaplan-Meier curves, log-rank tests, and Cox proportional hazards regression.

Results and Discussion

The outcomes of this trial aim to improve smoking cessation rates in low- and middle-income countries (LMICs) and inform clinical decisions regarding the use of tobacco harm reduction (THR) products for quitting smoking. However, some challenges in the study design have been identified. One significant issue is the selection of intervention products. With the increasing variety of e-cigarette models available, there is limited evidence of their effectiveness and quality [29]. The efficacy and user acceptance of different e-cigarette models may yield varying results. Nicotine patches are widely used in NRT, and this trial will employ 21 mg nicotine patches to compare their effects against e-cigarettes. This will help determine if adverse effects are related to e-cigarette use.

Some users report that they need time to adjust to e-cigarettes before achieving satisfaction, and research has shown that beginners often experience higher nicotine levels due to e-cigarette use [30]. To mitigate this, participants will receive detailed, illustrated instructions on how to use e-cigarettes and will be required to practice using them for a week before beginning their quit attempt. The trial will follow participants for 12 weeks, during which both efficacy and safety will be evaluated. This duration is considered sufficient to capture any unreported adverse effects. The findings will contribute valuable insights to the Cochrane systematic review on e-cigarettes for smoking cessation and reduction [31].

Conclusion

This randomized controlled trial aims to evaluate the safety and efficacy of tobacco harm reduction products within the adult population of low- and middle-income countries (LMICs). The outcomes of this research are expected to expand and enhance the current body of evidence advocating for the use of e-cigarettes in smoking cessation.

Acknowledgments: None

Conflict of Interest: None

Financial Support: The trial protocol was developed with funding from the Foundation for Smoke-Free World Inc., USA (Grant Number: W3-030).

Ethics Statement: The protocol has received approval from the Ethical Board Review Committee at South East Hospital and Research Centre, Islamabad, Pakistan (P23REC120).

References

1. Kumar N, Janmohamed K, Jiang J, Ainooson J, Billings A, Chen GQ, et al. Tobacco cessation in low-to middle-income countries: a scoping review of randomized controlled trials. Addict Behav. 2021;112(3):106612.
2. Sinha DN, Gupta PC, Kumar A, Bhartiya D, Agarwal N, Sharma S, et al. The poorest of poor suffer the greatest burden from smokeless tobacco use: a study from 140 countries. Nicotine Tob Res. 2018;20(12):1529-32.
3. Sreeramareddy CT, Harper S, Ernstsen L. Educational and wealth inequalities in tobacco use among men and women in 54 low-income and middle-income countries. Tob Control. 2018;27(1):26-34.
4. Theilmann M, Lemp JM, Winkler V, Manne-Goehler J, Marcus ME, Probst C, et al. Patterns of tobacco use in low and middle income countries by tobacco product and sociodemographic characteristics: nationally representative survey data from 82 countries. BMJ. 2022;378:e067582.
5. Jerzyński T, Stimson GV, Shapiro H, Król G. Estimation of the global number of e-cigarette users in 2020. Harm Reduct J. 2021;18(1):109.

6. Ghebreyesus TA. Progress in beating the tobacco epidemic. Lancet. 2019;394(10198):548-9.
7. Reitsma MB, Fullman N, Ng M, Salama JS, Abajobir A, Abate KH, et al. Smoking prevalence and attributable disease burden in 195 countries and territories, 1990–2015: a systematic analysis from the global burden of disease study 2015. Lancet. 2017;389(10082):1885-906.
8. Ward KD. Tobacco intervention research in low-and middle-income countries: lessons learned and future directions. J Smok Cessat. 2016;11(2):61-4.
9. Asfar T, Ward KD, Al-Ali R, Maziak W. Building evidence-based tobacco treatment in the Eastern Mediterranean region: lessons learned by the Syrian center for tobacco studies. J Smok Cessat. 2016;11(2):116-23.
10. Batmanghelidj E, Heydari G. Sanctions, smuggling, and the cigarette: the granting of Iran office of foreign asset control's licenses to big tobacco. Int J Prev Med. 2014;5(2):138.
11. Ahmadi J, Ashkani H, Ahmadi M, Ahmadi N. Twenty-four week maintenance treatment of cigarette smoking with nicotine gum, clonidine and naltrexone. J Subst Abuse Treat. 2003;24(3):251-5.
12. Zain Z. Roles of the private sector in tobacco cessation programmes. Addiction. 2002;97(8):960-1.
13. Rosser A. Contesting tobacco-control policy in Indonesia. Crit Asian Stud. 2015;47(1):69-93.
14. Lee SH, Ahn SH, Cheong YS. Effect of electronic cigarettes on smoking reduction and cessation in Korean male smokers: a randomized controlled study. J Am Board Fam Med. 2019;32(4):567-74.
15. Zhao SZ, Wu YS, Chau SL, Fong DYT, Lam TH, Wang MP. Mobile chat-based support plus nicotine replacement therapy sampling to promote smoking cessation for community smokers: a randomized controlled trial. Tob Induc Dis. 2021;19:32.
16. Rosner A. Fables or foibles: inherent problems with RCTs. J Manipulative Physiol Ther. 2003;26(7):460-7.
17. Morrison K. Randomised controlled trials for evidence-based education: some problems in judging 'what works'. Eval Res Educ. 2001;15(2):69-83.
18. Hughes JR. Tobacco control funding versus scientific evidence. Am J Prev Med. 2007;32(5):449-50.
19. Henningfield JE, Fant RV, Buchhalter AR, Stitzer ML. Pharmacotherapy for nicotine dependence 1. CA Cancer J Clin. 2005;55(5):281-99.
20. George TP. Nicotine and tobacco. InGoldman's Cecil medicine 2012 Jan 1 (pp. 142-146). WB Saunders.
21. Lovinger RD. Addiction medicine: an introduction for health care professionals. Elsevier Health Sciences; 2019.
22. Vansickel AR, Cobb CO, Weaver MF, Eissenberg TE. A clinical laboratory model for evaluating the acute effects of electronic “cigarettes”: nicotine delivery profile and cardiovascular and subjective effects. Cancer Epidemiol, Biomarkers Prev. 2010;19(8):1945-53.
23. Hébert-Losier A, Filion KB, Windle SB, Eisenberg MJ. A randomized controlled trial evaluating the efficacy of e-cigarette use for smoking cessation in the general population: E3 trial design. CJC Open. 2020;2(3):168-75.
24. Rafful C, García-Rodríguez O, Wang S, Secades-Villa R, Martínez-Ortega JM, Blanco C. Predictors of quit attempts and successful quit attempts in a nationally representative sample of smokers. Addict Behav. 2013;38(4):1920-3.
25. Al-Delaimy WK, Myers MG, Leas EC, Strong DR, Hofstetter CR. E-cigarette use in the past and quitting behavior in the future: a population-based study. Am J Public Health. 2015;105(6):1213-9.
26. Biener L, Hargraves JL. A longitudinal study of electronic cigarette use among a population-based sample of adult smokers: association with smoking cessation and motivation to quit. Nicotine Tob Res. 2015;17(2):127-33.
27. Adriaens K, Belmans E, Van Gucht D, Baeyens F. Electronic cigarettes in standard smoking cessation treatment by tobacco counselors in Flanders: e-cigarette users show similar if not higher quit rates as those using commonly recommended smoking cessation aids. Harm Reduct J. 2021;18(1):28.
28. Myers Smith K, Phillips-Waller A, Pesola F, McRobbie H, Przulj D, Orzol M, et al. E-cigarettes versus nicotine replacement treatment as harm reduction interventions for smokers who find quitting difficult: randomized controlled trial. Addiction. 2022;117(1):224-33.
29. Rodgers A, Corbett T, Bramley D, Riddell T, Wills M, Lin RB, et al. Do u smoke after txt? Results of a randomised trial of smoking cessation using mobile

phone text messaging. Tob Control. 2005;14(4):255-61.

30. Caponnetto P, Polosa R, Auditore R, Russo C, Campagna D. Smoking cessation with e-cigarettes in smokers with a documented history of depression and recurring relapses. Int J Clin Med. 2011;2(03):281.
31. Thornton SL, Oller L, Sawyer T. Fatal intravenous injection of electronic nicotine delivery system refilling solution. J Med Toxicol. 2014;10(2):202-4.