Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 5, 2021, Pages. 3525 - 3534
Received 15 April 2021; Accepted 05 May 2021.

A Randomized Trial Protocol to Determine Effectiveness of Nicotine Replacement Therapy on Smoking Cessation of Tuberculosis Patients in Coastal India

[1]Jagannath Purushothama, [2]Sanjeev Badiger,

[1]K S Hegde Medical Academy, Nitte (Deemed to be University), Mangaluru, India

[2]Head, Department of Community Medicine, A J Institute of Medical Sciences and Research Centre, Mangaluru, India.

Corresponding author: Sanjeev Badiger

Running title: Effectiveness of Nicotine Replacement Therapy- A Randomized Trial

Keywords: Smoking cessation; clinical trial protocols as topic; tuberculosis; pulmonary; India

Abstract:

Background: Tobacco smoking and pulmonary tuberculosis combined is two preventable public health concerns. They put the annual global death rates from these two diseases at over six million. There is tangible evidence from studies conducted on more than forty thousand patients regarding nicotine therapy for tobacco smokers enhances likelihood of success when compared to support without nicotine replacement. This study determines the effectiveness of nicotine replacement therapy among tuberculosis patients.

Methods: This protocol study determines the effectiveness of tobacco smoking cessation rates among pulmonary tuberculosis patients on nicotine replacement treatment. The secondary objectives are to determine the relationship between smoking cessation and tuberculosis treatment outcome and the determinants of smoking cessation. This CONSORT 2010 checklist-based, placebo controlled, block- randomized, double-arm, single blind trial will be experimented between March 2019 and August 2022 in Mangaluru, India, with a sample size of 300 in both the arms. The intervention group will be prescribed with nicotine polacrilex chewing gums along with brief advice and the control group with brief advice and sugar-free chewing gum as a placebo for three months in a tapered dose with 3 months of follow-up. The binary outcome of reported status of smoking the participants will be confirmed by urine cotinine qualitative test at the start and end of the trial apart from monthly carbon monoxide monitoring and Fagerstorm scoring. Ethical clearance is obtained from Nitte University.

Discussion: The collected information will be summarized by using frequencies and percentages for qualitative data, mean and standard deviation for quantitative data. To compare the outcome measures, quantitative, before and after intervention, paired-t test will be used. If the study has missing data more than 10% of the total sample size as expected during sample size calculation, Pattern-Mixture Model within a mixed-effects logistic regression model for longitudinal dichotomous data will be used. The significance of this study is to gather further evidence nicotine replacement therapy as an appropriate technology in primary care settings and further upwards by conducting the trial in actual healthcare settings.

Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 5, 2021, Pages. 3525 - 3534
Received 15 April 2021; Accepted 05 May 2021.

Trial registration: The trial is registered prospectively with the Clinical Trials Registry of India vide CTRI/2018/11/016457 dated 28/11/2018.

Introduction:

Tobacco smoking and pulmonary tuberculosis (TB) are major public health problems in the developing world posing as a considerable threat with annual global deaths exceeding six million [1]. Incredibly, tuberculosis and smoking are co-prevalent in low- and middle-income countries that synergistically cause higher morbidity and mortality [2]. It is less recognized that there is an association between tobacco smoking and natural history of pulmonary tuberculosis and poor TB treatment outcomes [3]. Prevalence of tobacco smoking among pulmonary tuberculosis patients is greater in comparison with non-tuberculosis individuals. Tobacco smoking increases the risk of latent tuberculosis by 1.9 times and active tuberculosis by 2 times and case-fatality rate by 2.6 times when adjusted for socio-economic status [4]. Smoking patients with active TB presented increased cavitary lesions (Odds ratio OR: 1.88; 95%CI:1.02–3.46;$p<0.05$). Also, latent TB infection was favored in smoking contacts, being a risk factor associated with infection (OR: 11.57; 95% CI: 5.97–22.41; $p<0.05$) [5].

It is documented that tobacco smoking conquers cell-mediated and humoral immunity that eventually causes TB infection and worsens treatment outcomes. Nevertheless, most immunological abnormalities induced by tobacco smoking reverse in less than six weeks after tobacco cessation. Thus, it is imperative that smoking cessation be amalgamated as a standard therapy along with anti-tubercular treatment for tobacco users especially smokers [6].

There is tangible evidence from studies conducted on more than forty thousand patients regarding nicotine therapy for tobacco smokers enhances likelihood of success when compared to support without nicotine replacement [7].Nicotine Replacement Therapy (NRT) has been effective in promoting abstinence rates even at short term abstinence for two weeks (OR = 2.02, 95% CI= 1.11–3.69) which reduced at the end of treatment (OR= 0.79, 95% CI= 0.57- 2.65) however with significant abstinence seen in high compliant participants [8]. Systematic reviews support this evidence that NRT is effective when compared to placebo or no intervention (OR=1.77; 95% (CI), 1.63 to 1.91) [9]. To address this research question, a two-armed, non-inferiority, placebo-controlled randomized trial is designed. The study gathers further evidence to portray the effectiveness of brief advice with nicotine replacement therapy for smoking cessation in real-life low-middle income country settings. The study contemplates dropout rates and their alternative statistical analyses based on missing data expected out of the trial and this protocol paper also comes in handy for future researchers intending to design a protocol for similar studies. This study aims to determine the effectiveness of brief advice aided nicotine replacement therapy on smoking cessation among pulmonary tuberculosis patients registered for anti-tubercular treatment in Dakshina Kannada District of Karnataka State, India.

Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 5, 2021, Pages. 3525 - 3534
Received 15 April 2021; Accepted 05 May 2021.

Methods:

A. Trial Design: This randomized, placebo-controlled, two-armed, single-blinded trial is designed based on CONSORT 2010 Guidelines [11]. The study began in January 2019 as part of the principal investigator's PhD thesis under the aegis of Nitte (deemed to be University), Mangaluru, India, in partnership with National Health Mission, Dakshina Kannada District, Government of Karnataka.The primary objective of the study is to determine the effectiveness of nicotine replacement therapy on smoking cessation among the pulmonary tuberculosis patients. The most apt study design for fulfilling this objective would be to conduct a randomized controlled trial. The nicotine replacement therapy was considered as the intervention because this study is being conducted on the target population of pulmonary tuberculosis patients undergoing anti-tubercular treatment for duration of six months. This intervention time can be simultaneously utilized for nicotine replacement therapy (NRT) that aims to reduce motivation to smoke and the physiological and psychomotor withdrawal symptoms often experienced during an attempt to stop smoking, and therefore increase the likelihood of remaining abstinent [12]. The study design is a randomized, placebo-controlled parallel superiority trial with 1:1 allocation ratio. This superiority trial intends to gather further evidence that nicotine replacement therapy with brief advice is more efficient than brief advice alone which is now currently practiced in the Revised National Tuberculosis Control Program (RNTCP) renamed as National Tuberculosis Elimination Program (NTEP). Hence brief advice is coupled with a placebo in the form of a mint- flavored sugar-free chewing gum for the control group. The study period is between January 2019 and August 2020. Pediatric TB, mono or Multi-Drug Resistant TB patients, participants not willing to quit smoking following brief advice, participants not willing to participate in the study, smokeless tobacco users, patients contraindicated for NRT: (recent history of myocardial infarction, angina; pregnancy & lactation) will be excluded from the trial before recruitment. Participants who quit smoking within 4 weeks of the trial would be excluded from the trial since it may be a confounder for smoking cessation due to NRT. This is because when duration of NRT use was considered, it was found that persons who used NRT for less than four weeks were less likely to quit according to Zhang et.al [13].

B. **Study Setting:**

The study is conducted at the Tobacco Cessation Centre, Wenlock Hospital, Mangaluru, India. Wenlock Hospital is the tertiary level Government-owned District level hospital with more than 700 beds that also has an exclusive tobacco cessation centre that provides services to 200 to 250 patients on a monthly basis with free nicotine replacement therapy and counseling services. Patients and/or visitors of this hospital who are known tobacco users will be advised to take services at the tobacco cessation centre to quit tobacco. A full-time psychologist provides the counseling services and a qualified medical practitioner prescribes nicotine replacement therapy. However, until date, tuberculosis patients were neither referred to the centre nor were assessed for tobacco use by either history-taking or diagnostic tests. Through this study, enrolment of pulmonary tuberculosis patients for a brief advice was arranged with an objective to recruit the smokers for the study. The estimated completion date of the study is August 2021. Follow-up of the participants will be done at the nearest Primary Health Centre/Taluk Hospital for the participants on a monthly basis.

Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 5, 2021, Pages. 3525 - 3534
Received 15 April 2021; Accepted 05 May 2021.

C. **Participants:**

The smoking cessation trial aims to recruit 150 participants in each arm. The participants will be selected based on the eligibility and exclusion criteria. All eligible participants registered under Nikshay TB portal who walk in for treatment or diagnosis that have not completed more than one month of Directly Observed Therapy Short Course (DOTS) will be registered for the study. Participants will be recruited based on the eligibility criteria of microbiologically confirmed or clinically diagnosed pulmonary TB cases with a history of smoking tobacco in the past one year. The participant information sheet will be given and explained to the participant by the investigator about the risks and benefits of participating in the trial.

D. Intervention and Control arm:

Intervention for the experimental Group will be NRT containing 2 mg nicotine chewing gums for 3 months with tapering dosage pattern along with monthly brief advice (5 A's). The control Group will be given non nicotine chewing gums (placebo) for 3 months with tapering dosage pattern along with monthly brief advice (5 A's). The 5As (Ask, Advise, Assess, Assist, Arrange) summarize all the activities that a primary care provider can do to help a tobacco user within 3−5 minutes in a primary care setting. This model can guide through the right process to talk to patients who are ready to quit about tobacco use and deliver advice [14]. Carbon monoxide (CO) monitor will be used toassess the exhaled CO level of the study participants. The cutoff point will be six parts per million or less for nonsmokers and more than six parts per million for smokers [15]. Urine cotinine test will be done to assess the smoking status of the participants during baseline and end-line of the study. These two clinical risk endpoints were chosen for their evidence to demonstrate the smoking status and their favorable change upon smoking cessation within a timeframe feasible for the study duration [16]. Participants who were not eligible for the study were referred to the tobacco cessation center at the District hospital for routine intervention. Two research assistants with prior work experience in tuberculosis control program are recruited and trained to provide brief advice to the study participants and prescription of the intervention to both the arms. The participants were informed to visit the primary health center on a monthly basis to administer the intervention. After three months of intervention, another three months was allocated for follow-up that involved only brief advice. Participants who continue the use of NRT/placebo after 3 months of intervention will be counseled for discontinuation within one month of follow-up. Further use of NRT/placebo will be classified as “prolonged use”.

E. **Primary Outcomes:**

The primary clinical outcome will be the binary smoking abstinence or non-abstinence assessed at 3 months after intervention and 3 months after follow-up. Non-abstinence will be defined as self-reported seven or more consecutive days of smoking since the end of intervention or smoking over the two consecutive weeks prior to the assessment or positive urine cotinine test at the end of three months of follow-up.

F. Secondary outcomes:

Secondary outcomes of interest at the final followup will includenumber of quit attempts since enrollment, the number of smoked cigarettes/bidis per day (for those who were not able to quit), duration of use of intervention. The final outcomes will be smoking excess, smoking reduction,

Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 5, 2021, Pages. 3525 - 3534
Received 15 April 2021; Accepted 05 May 2021.

continued use and relapse from the baseline information.

G. **Sample size:**

In a study conducted to find the efficacy of smoking cessation at tuberculosis clinics in Tshwane, South Africa, self-reported 6-month sustained abstinence was 21.5% for the intervention group and 9.3% for the control group with a level of significance of 5%, power of 80% in the two-sided test [17]. This result was considered to calculate the sample size for the current study. As a result, the sample size therefore in each arm is 136. By considering a loss to follow up of 10% in each arm, the sample size is 149.6 rounded off to 150 per arm.

H**. Randomization, blinding, and allocation concealment:**

When planning a randomized clinical trial, careful caution must be executed in selection of participants for various arms of the study. Selection and accidental bias may occur when participants are not assigned to study groups with equal probability [12]. Hence, block Randomization was done to obtain the two groups using a computer-generated table. Each block contains four participants in a unique sequence of experimental arm and control arm of 82 blocks. In the experimental group study participants will be given nicotine replacement therapy and brief advice; and in the control group brief advice as per National Framework for joint TB-Tobacco collaborative activities and non-nicotine chewing gums (placebo) will be provided. The trial will be single-blinded wherein the participant will not be aware of the group that they belong to. Concealment will be ensured ineach participant's group allocation by a sealed envelope with the identity number labeled on the envelope. The packaging of the chewing gums for both the groups will be made using plain and sterile drug container boxes.

I**. Tool development:**

A semi-structured questionnaire was developed to capture information about the participants' socio-demographic factors, smoking history, current smoking status, tobacco dependence score, diagnosis of tuberculosis, follow-up of treatment, and stage of transtheoretical model during each visit on a monthly basis. The participants will be assessed for carbon monoxide levels, body weight in kg and urine cotinine test during the start and end of the follow-up. This questionnaire was tested among 10 participants of the TB Sanatorium of Dakshina Kannada District located in Moodushedde of Mangaluru City.

J. **Statistical Analysis:**

The collected information will be summarized by using frequency and percentage for qualitative data, mean and standard Deviation for quantitative data. To compare the outcome measures, quantitative before and after intervention, paired-t test will be used. If data is not following normal distribution, Wilcoxan Signed Rank test will be used. To compare qualitative outcomes, Chi-square test or Fischer exact test will be used.To compare the difference in outcome measures between two intervention groups, independent sample't' test will be used.If data is not following

Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 5, 2021, Pages. 3525 - 3534
Received 15 April 2021; Accepted 05 May 2021.

normal distribution, Mann Whitney test will be used. To determine the association between the binary tuberculosis outcomes and binary cessation outcome, odds ratio will be applied. The P value less than 0.05 will be considered as statistically significant.

Results:

The collected information will be summarized by using frequencies and percentages for qualitative data, mean and standard deviation for quantitative data. To compare the outcome measures, quantitative, before and after intervention, paired-t test will be used. If data is not following normal distribution, Wilcoxan Signed Rank test will be used. To compare qualitative outcomes, Chi-square test or Fischer exact test will be used. To compare the difference in outcome measures between two intervention groups, independent sample‘t’ test will be used. If data is not following normal distribution, Mann Whitney test will be used. ‘p’ value less than 0.05 will be considered as statistically significant [18]. The study shall adopt the “Intention to Treat Analysis” mechanism. If the study has missing data more than 10% of the total sample size as expected during sample size calculation, Pattern-Mixture Model within a mixed-effects logistic regression model for longitudinal dichotomous data will be used. Because of the dichotomous outcome, logistic regression version of the mixed-effects model is applicable. The pattern-mixture effects for drug, time, data pattern and their interactions will be interpreted. Pattern mixture sensitivity analysis using SAS/STAT, missing data analysis will be done using R software, and survival analysis will be used to analyze the variation in smoking relapse over time related to the socio-demographics, smoking history, and treatment-related variables.

Discussion:

Tuberculosis, an infectious disease caused by Mycobacterium Tuberculosis is a major public health problem in different parts of India. The disease primarily affects lungs and causes pulmonary tuberculosis [19] [20]. It is the second greatest killer due to a single infection agent worldwide, about one-third of the world, population is believed to have latent TB [21]. Tuberculosis is one of the world’s oldest diseases dating back to 4000 years ago recognized by Indian civilizations [22]. This randomized trial purports to study the effectiveness of nicotine replacement therapy on smoking cessation of pulmonary tuberculosis patients. The significance of this study is to gather further evidence about the use of nicotine replacement therapy as an appropriate technology that can be used in primary care settings and further upwards by conducting the trial in actual healthcare settings. Two national health programs namely National Tuberculosis Elimination Program and National Tobacco Control Program are operational in India vertically with minimal interrelationship. However, there is a goldmine of opportunity for the integration of these two programs given the fact that the duration of treatment for both the diseases has a prolonged duration and requires supervision by healthcare workers apart from family members. The most effective method for smoking cessation is nicotine replacement therapy which has wider acceptance among the general population. Hence this trial incorporated a study design of Randomized Controlled Trial (RCT) to prove the effectiveness of nicotine replacement therapy with brief advice over brief advice alone. To rationalize the intervention and control arm, latter has been added with a placebo chewing gum to match with nicotine chewing gum in the intervention arm. The intervention is for three months followed by another three months of follow up. This binary outcome study will bifurcate the participants into abstinent and

Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 5, 2021, Pages. 3525 - 3534
Received 15 April 2021; Accepted 05 May 2021.

non-abstinent persons at the end of the follow up. Secondary outcomes such as smoking reduction, smoking excess, relapse will be assessed in terms of smoking factors. Treatment status and tuberculosis outcomes will be assessed for additional evidence and correlation with the primary outcomes. This study also gathers evidence about the TB treatment outcome and its relationship with smoking cessation status. This study is purported to be one among the very few similar studies conducted in India that incorporates urine cotinine test as the standard biomarker to determine the cessation outcome. Furthermore, the study will be conducted in the Government health facilities by recruiting participants from these setups so as to blend the study findings with translational research. The limitations of the study are the standard treatment regimen for all the participants irrespective of the possible variance in the bioavailability of the nicotine replacement drug. Customized dosage and extension of the treatment duration will not be considered in the study. Single blinding is adopted in the study owing to limited financial and human resources.

Conclusions:

This study focuses on determining the effectiveness of nicotine replacement therapy on smoking cessation of pulmonary tuberculosis patients undergoing DOTS treatment. The study results shall add scientific evidence to the available literature about the nicotine replacement therapy being an effective intervention that brief advice alone. The study protocol through publication in leading journals assists future researchers in this area of interest to adopt certain or most of the aspects of the study protocol relevant to their methodology and research setup.

List of abbreviations:

[CO: Carbon Monoxide

CI: Confidence Interval

DOTS: Directly Observed Therapy Short Course

NRT: Nicotine Replacement Therapy

NTEP: National Tuberculosis Elimination Program

OR: Odds Ratio

P: probability

RCT: Randomized Controlled Trial

RNTCP: Revised National Tuberculosis Control Program

TB: Tuberculosis

Declarations:

Ethics approval and consent to participate

Approval is obtained from the Institutional Central Ethics Committee, Nitte (Deemed to be University), (NU/CEC/2019/209 dated 30th January 2019). The study is registered with the Clinical Trials Registry of India (CTRI/2018/11/016457 dated 1st December 2018).

Administrative approval was obtained from theDistrict Health and Family Welfare Society. Participation in the study will be voluntary and written informed consent will be obtained by the study participants. Participants are free to withdraw from the study at any point of time. All the participants will be given brief advice. Control group will be given standard treatment after completion of the trial. Side effects if any will be reported to the ethics committee and arranged for management at the Hospital. The cost of treatment will be borne by the investigator. The study has no conflict of interest during any stage of the trial.

Consent for publication: The manuscript does not contain any individual person's data in any form such as individual details, images, or videos.

Availability of data and materials: The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests: The authors declare that they have no competing interests.

Funding: Funding was obtained for the study from National Tobacco Control Program, Dakshina Kannada.

Authors' contribution:

JP- Conception; design of the work; data collection; literature review; analysis; interpretation of data; writing.

SB: Conception; design of the work; supervision; critical review; proof reading.

All the authors have read and approved the manuscript.

Acknowledgements: The authors thank the Institutional Ethics Committee for their valuable guidance throughout the conception of the study.

References

1. Gegia M, Magee J M, Kempker R R, Kalandadze L, Chakhaia T, Golub E J et.al. Tobacco smoking and tuberculosis treatment outcomes: a prospective cohort study in Georgia. Bull World Health Organ. [Internet]. 2015 [cited 2020 February 13]; 93(6): 390–99. Available from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4450709/. PMID: 26240460
2. Aryanpur M, Hosseini M, Mazjedi R M, Mortaz E, Tabarsi P, Soori H et al. A randomized controlled trial of smoking cessation methods in patients newly diagnosed with pulmonary tuberculosis. BMC Infect. Dis. [Internet]. 2016 [cited 2020 January 28]; 16(369):2-9. Available from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4974814/. PMID: 27496096
3. Smit Z, Pai M, W.W. Yew, Leung C.C, Zumla A, Bateman E D et.al. Global lung health: the colliding epidemics of tuberculosis, tobacco smoking, HIV and COPD. Eur Respir J. [Internet] 2010 [cited 2020 January 28]; 35(1): 27–33. Available from https://pubmed.ncbi.nlm.nih.gov/20044459/. PMID: 20044459
4. Mahishale V, Patil B, Lolly M, Eti A and Khan S. Prevalence of Smoking and Its Impact on Treatment Outcomes in Newly Diagnosed Pulmonary Tuberculosis Patients: A Hospital-Based Prospective Study. Chonnam Med J. [Internet] 2015 [cited 2020 August 26]; 51: 86-90.

Available from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4543154/5.

5. Altet N, Latorre I, Jime ´nez-Fuentes MA ´, Maldonado J, Molina I, Gonza ´lez-Dı ´az Y, et al. Assessment of the influence of direct tobacco smoke on infection and active TB management. PLoS ONE 12[Internet] 2017 [cited 29 October 2020]. Available from: e0182998.https:// doi.org/10.1371/journal.pone.01829986.

6. Awaisu A, Mohamed NHM, Noordin M N, Aziz A N, Sulaiman S A S, Muttalif R A. The SCIDOTS Project: Evidence of benefits of an integrated tobacco cessation intervention in tuberculosis care on treatment outcomes. Subst Abuse Treat Prev Policy [Internet]. 2011; [cited 2020 August 26] 6:26. Available from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3196696/

7. Stead LF, Perera R, Bullen C, Mant D, Lancaster T. Nicotine replacement therapy for smoking cessation. Cochrane Database Syst Rev [Internet]. 2012; [cited 2020 January 01] Available from 10.1002/14651858.CD000146.pub4

8. Scherphof CS, van den Eijnden RJ, Engels RC, Vollebergh WA. Short-term efficacy of nicotine replacement therapy for smoking cessation in adolescents: a randomized controlled trial. Journalof Substance Abuse Treatment. [Internet].2014 [cited 2020 January 01] Available from: https://europepmc.org/article/med/24029624. PMID: 24029624

9. Woolacott NF, Jones L, Forbes CA, Mather LC, Sowden AJ, Song FJ et.al. The clinical effectiveness and costeffectiveness of bupropion and nicotine replacement therapy for smoking cessation:a systematic review and economic evaluation. Health Technol Assess [Internet] 2002 [cited 29 October 2020]. Available from: https://pubmed.ncbi.nlm.nih.gov/12269277/ [PMID: 12269277]

10. Pandey A. K., Singh R. J., Swasticharan L. National framework on TB-Tobacco collaborative activities: most cost-effective way to manage TB-Tobacco comorbidity and extend tobacco cessation services. Tobacco Induced Diseases. 2018;16(1):829. doi:10.18332/tid/84476.

11. Schulz K F, Altman D G, Moher D. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials. BMC Medicine [Internet] 2010[cited 29 October 2020]. Available from: https://bmcmedicine.biomedcentral.com/articles/10.1186/1741-7015-8-18

12. Efird J. Blocked Randomization with Randomly Selected Block Sizes. Int. J. Environ. Res. Public Health. [Internet] 2011 [Cited 2020 January 28]; 8 (1): 15-20. Available from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3037057/

13. Zhang B, Cohen E J, Bondy J S, Selby P. Duration of Nicotine Replacement Therapy Use and Smoking Cessation: A Population-Based Longitudinal Study. Am J Epidemiol. [Internet] 2015 [cited 2020 January 01] Available from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4371764/

14. World Health Organization. Toolkit for delivering the 5A's and 5R's brief tobacco interventions in primary care. Geneva. [Internet] 2014. [cited 2020 August 26] Available from http://www.who.int/tobacco/publications/smoking_cessation/9789241506953/en

15. Xavier LEDF, Bernardes-Souza B, Lisboa OC, Seeger W, Groneberg DA, Tran TA et al. A Medical Student–Delivered Smoking Prevention Program, Education Against Tobacco, for Secondary Schools in Brazil: Study Protocol for a Randomized Trial. JMIR Res Protoc 2017; 6(1): e16.

Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 5, 2021, Pages. 3525 - 3534
Received 15 April 2021; Accepted 05 May 2021.

16. Ansari SM, Lama N, Blanc N, Bosilkovska M, Donelli A, Picavet P et.al. Evaluation of Biological and Functional Changes in Healthy Smokers Switching to the Tobacco Heating System 2.2 Versus Continued Tobacco Smoking: Protocol for a Randomized, Controlled, Multicenter Study JMIR Res Protoc [Internet] 2018 [cited on 29 October 2020]. Available from: https://pubmed.ncbi.nlm.nih.gov/30143474/

17. Louwagi G M, Okuvemi KV, Yusuf OA. Efficacy of brief motivational interviewing on smoking cessation at tuberculosis clinics in Tshwane, South Africa: a randomized controlled trial. Addiction. [Internet] 2014 [Cited 2020 January 30]; 109(11):1942-52. Available from http://doi.wiley.com/10.1111/add.12671

18. Brinker TJ, Owczarek AD, Seeger W, Groneberg DA, Brieske CM, Jansen P, Klode J, Stoffels I, Schadendorf D, Izar B, Fries FN, Hofmann FJ A Medical Student-Delivered Smoking Prevention Program, Education Against Tobacco, for Secondary Schools in Germany: Randomized Controlled Trial J Med Internet Res 2017;19(6): e199 URL: http://www.jmir.org/2017/6/e199/. [PMID: 28588007]

19. Singha A. Tuberculosis in post-colonial Birbhum; through the eyes of gender differences." International Journal of Research in Applied, Natural and Social Sciences. 2015: 3 (9); 73-76.

20. Chaurasia R N, Jaiswal S, Mishra V N, Joshi D. Great auricular nerve tuberculosis: case report and review. International Journal of General Medicine and Pharmacy. 2015: 4 (6); 9-12

21. Al-Tmem M B, Khalid. Al. Fartosi K G, Al-Farhan N F M. The Association of HLA-DRB1 & DQB1 alleles and Haplotype Frequency in Iraqi patient with Pulmonary Tuberculosis in Thi-Qar Province, Iraq. 2015: International Journal of Research in Applied, Natural and Social Sciences. 2015: 3 (11); 39-50.

22. Chug A, Mehra P, Shukla S. Tuberculosis of the zygomatic bone–A rare entity. International Journal of Dental Research & Development. 2018: 8 (1); 5-8.

23. Brooks. R M. Role of smoke alarms in fire disaster prevention management for homes. International Journal of Humanities and Social Sciences. 2018: 7 (3); 1-4.