International Journal of Clinical Trials
Green HJ et al. Int J Clin Trials. 2022 May;9(2):136-142
http://www.ijclinicaltrials.com
pISSN 2349-3240 | eISSN 2349-3259

DOI: https://dx.doi.org/10.18203/2349-3259.ijct20221114

Protocol

An exploratory, randomised, crossover study to investigate the effect of nicotine on cognitive function in healthy adult smokers who use an electronic cigarette, after a period of smoking abstinence: study protocol

Harry Jacob Green[1]*, Olivia Katherine O'shea[1], Helen Louise Philpott[2], Nik Newland[1]

[1]BAT, New Sciences, R&D, Southampton, United Kingdom
[2]Simbec-Orion, Merthyr Tydfil, United Kingdom

Received: 27 February 2022
Revised: 07 March 2022
Accepted: 31 March 2022

***Correspondence:**
Harry Jacob Green,
E-mail: harry_green@bat.com

ABSTRACT

Background: Despite the known harmful effects of cigarette smoking, many individuals continue to smoke. Published scientific evidence suggests that smoking can influence various physiological and psychological functions (including effects on cognitive function, body weight and emotion). For some smokers, the loss of such effects have been cited as barriers to cigarette smoking cessation and the deficits in such effects may contribute to resumption of smoking post quitting. Whilst not positioned as cigarette cessation devices, the effect of e-cigarettes (and other potentially reduced risk alternatives to cigarette smoking) on such functions has not been widely researched. Such information would provide support for the proposition that smokers seeking alternatives may find e-cigarettes a satisfactory substitute for conventional cigarettes.
Methods: This randomised, partially blinded, crossover study will test the hypothesis that acute nicotine delivery via an e-cigarette can influence cognitive parameters including sustained attention, episodic memory, working memory and executive function to the same extent as a combustible cigarette after a period of nicotine abstinence in current smokers. To determine participants' cognitive ability, the study will utilise the Cambridge Neuropsychological Test Automated Battery (CANTAB) Connect Profile Software (CANTAB® www.cantab.com). Up to 40 current smokers will be recruited into the study.
Conclusions: The data from this trial will be a valuable addition to the growing body of literature assessing the impact of RRPs for existing smokers.
Trial registration: This study is registered with the ISRCTN registry, number ISRCTN35376793.

Keywords: Nicotine, E-cigarette, Cognitive function, Smoking cessation, Tobacco harm-reduction

INTRODUCTION

It is well understood that cigarette smoking is a leading avoidable cause of disease, including cardiovascular disease, lung disease and cancer. Whilst there has been a global decline in smoking prevalence, the health burden associated with smoking remains high.[1] As such, as part of a global public health priority, various regulatory and educational tobacco control initiatives have been launched aimed at reducing the negative health burden of combustible tobacco use.[1] Despite such efforts, smoking rates in adult populations remain at 10-40% in most countries, with the WHO reporting that there are still in excess of 1 billion tobacco smokers worldwide.[1,2] As an additional tool for tobacco control, therefore, interest has grown in the concept of tobacco harm reduction (THR), which is a public health strategy that aims to reduce or prevent the harm caused by smoking. Commonly, THR

involves the substitution of cigarette smoking with reduced-risk nicotine products (RRPs) such as tobacco heating products (THPs) and electronic cigarettes (e-cigarettes).[3]

E-cigarettes (also termed electronic nicotine delivery systems (ENDS)) deliver nicotine (and/or flavour) in an aerosolised carrier, most frequently comprising vegetable glycerine and propylene glycol, without tobacco or combustion.[3] A number of studies have demonstrated that e-cigarette aerosol contains significantly fewer and lower levels of chemical toxicants than cigarette smoke.[4-5] Both the UK Royal College of Physicians and Public Health England have extensively reviewed the scientific evidence, aligning with opinion that e-cigarette use is approximately 95% less harmful than cigarette smoking.[7-9] The US National Academies of Sciences (NAS) also reviewed the available scientific data and concluded that, "while e-cigarettes are not without health risks, they are likely to be far less harmful than conventional cigarettes".[6] Despite the known harmful effects of cigarette smoking, successful cessation rates remain low (around 3% per year) and hence there is a need to further understand potential barriers to cessation and causes of cigarette resumption and their potential applicability to reduced risk alternatives such as e-cigarettes.[13]

As well as the aforementioned negative health outcomes, cigarette smoking is associated with a range of physiological and psychological effects such as effects on body weight, emotion and cognitive function.[10-12] Published scientific evidence suggests that smoking can affect numerous elements of cognitive function, including (but not limited to) sustained attention, working memory and executive function.[12] These effects have been demonstrated to be important to smokers, whilst deficits in cognitive function and other alterations such as post-cessation weight gain (PCWG) following smoking cessation have been cited as reasons for resumption of smoking.[14-17] Whilst not marketed as cigarette cessation devices, the effect of e-cigarettes (and other potentially reduced risk alternatives to cigarette smoking) on such functions has not been widely researched but may be important in the acceptability of e-cigarettes to existing smokers, encouraging smokers, who would otherwise continue to smoke, to switch to an RRP.

The research methodologies applied in this study have been utilised widely in adjacent research fields and the cognitive assessment tools have been previously demonstrated to be sensitive to acute improvements/impairments to a wide variety of interventions, including presence versus absence of nicotine.[21,22] The approach has not however been utilised extensively to research differences between nicotine-containing products and as such, the sensitivity of the approach to determine differences between nicotine containing products with different exposure routes, quantities and pharmacokinetic profile, has yet to be fully elucidated.

The aim of this study is to test the hypothesis that acute nicotine delivery via an e-cigarette can influence cognitive parameters including sustained attention, episodic memory, working memory and executive function to the same extent as a combustible cigarette after a period of nicotine abstinence in current smokers.

METHODS

A redacted version of the full study protocol and statistical analysis plan (SAP) is provided in the supplementary information, submitted with this manuscript. The key aspects of the protocol are summarised below.

Study design and participants

The study will be a single-centre, prospective, randomised, partially blinded, crossover study performed in a purpose-built trial facility at Simbec-Orion (Merthyr Tydfil, UK). Eligible participants will be healthy adult current smokers.

Inclusion criteria

For a complete list of the inclusion criteria please refer to the study protocol (see supplementary information). The inclusion criteria include:

Participants will be healthy male or female subjects, aged between 25-45 years (inclusive) and considered in good general health (as confirmed via the principal investigator (PI)). All participants will have a body mass index (BMI) between 18.5-29.9 kg/m^2 (inclusive). Participants will be current smokers (self-reported consumption of at least 10 factory-made or self-rolled cigarettes per day for 3 years or longer), with smoking status confirmed via urinary cotinine sample (≥200 ng/mL). Additionally, participants will be familiar with e-cigarettes (classified as use for at least 1 month in the previous 2 years). All participants will be required to adhere to the study protocol, including a willingness to abstain from smoking, nicotine products, alcohol and caffeine (for 12 hours) and high-intensity exercise (for 24 hours) prior to each study session.

Exclusion criteria

For a complete list of the exclusion criteria please refer to the study protocol, supplementary information.

The exclusion criteria include any participants who, prior to enrolment, are planning to quit/alter smoking/vaping usage within the duration of the study (to the follow-up telephone call). Participants with acute illness (e.g., respiratory tract infection, viral infection, positive COVID-19 PCR (Antigen) test prior to day 1, etc) requiring treatment within 4 weeks prior to screening or upon admission or evidence of renal, hepatic, central nervous system, respiratory, cardiovascular or metabolic dysfunction based on medical history will also be

excluded. Participants must not possess a clinically significant history of drug or alcohol abuse (defined as the consumption of more than 14 units of alcohol a week for male and female subjects) within the past two years or have been diagnosed with a clinically significant cognitive disorder (or have used central nervous system enhancing or modulating medications within the last 3 months, felt to be of clinical significance by the PI). Participants with a colour vision deficiency as determined by an Ishihara test performed at screening will also be excluded.

Randomisation and blinding

The randomisation schedule will be created by Simbec-Orion using a computer-generated pseudo-random permutation procedure in SAS version 9.4 and will determine the order in which participants are assigned to use each investigational product (or no product) during the study (Table 1). Codes will be produced based on Williams Latin square design for a five-by-five crossover with 10 sequences and four participants per sequence. Blinding will be applied to e-cigarette nicotine strength and will be maintained by participants being handed ready assembled devices.

Table 1: A table demonstrating the investigational products to be used within the study.

Product	Nicotine strength	Product usage
No product	N/A	N/A
E-cigarette	0 mg/ml	5 min *ad libitum*
E-cigarette	12 mg/ml	5 min *ad libitum*
E-cigarette	18 mg/ml	5 min *ad libitum*
Combustible cigarette	N/A*	1 stick 5 min *ad libitum*

Note: *7 mg ISO tar cigarette.

Investigational product

The e-cigarette investigational product (Vype ePen3) is a commercially available, closed-system e-cigarette with a 650 mAh rechargeable battery and associated 2.0 ml disposable cartridge containing e-liquid and a mouthpiece; manufactured on behalf of Nicoventures trading Ltd, London, UK (cartridges for use in the study were manufactured at BAT R&D, Southampton, UK to the commercial specifications). Each cartridge lasts for approximately 200 puffs with delivery of aerosol controlled to remain consistent throughout the charge/discharge cycle.

The product was selected in part due to the known pharmacokinetic profile (the start of cognitive testing has been aligned with the product TMax).[23] E-liquids used in the study will contain 0, 12, or 18 mg/ml nicotine (protonated) and will be golden tobacco flavour (Table 1).

All participants will receive a demonstration and training at screening on how to correctly use the e-cigarette investigational product.

The cigarettes to be used in the study will be commercially sourced Benson & Hedges sky blue king-size cigarettes, the market leading combustible cigarette in the UK (at time of study set-up).

Study objectives and endpoints

Primary objective

The primary objective of the study is to determine how acute delivery of nicotine delivered via an e-cigarette can influence aspects of cognitive function (sustained attention, working memory, episodic memory and executive function) in regular smokers following a 12-hour period of nicotine abstinence compared to a combustible cigarette.

Secondary objectives

The secondary objectives of this study are to determine how acute delivery of nicotine delivered via an e-cigarette can influence subjective emotion in regular smokers following a 12-hour period of nicotine abstinence compared to a combustible cigarette and to determine how acute delivery of nicotine delivered via an e-cigarette can influence subjective craving in regular smokers following a 12-hour period of nicotine abstinence compared to a combustible cigarette.

Study endpoints

Primary endpoints

Sustained attention as assessed via completion of the rapid visual information processing (RVP) task. Working memory as assessed via completion of the spatial working memory (SWM) task. Executive function as assessed via completion of the one touch stockings of Cambridge (OTS) task. Episodic memory as assessed via completion of the paired associates learning (PAL) task.

Secondary endpoints

Visual analogue scale subjective emotion questionnaire (eCOA). Questionnaire on Smoking Urges (QSU)-brief (eCOA).

Measurement tools

To determine participants' cognitive ability, the study will utilise the Cambridge Neuropsychological Test Automated Battery (CANTAB) Connect Profile Software (Cambridge Cognition, Cambridge, UK), a broad computerised assessment battery capable of assessing and characterising a wide range of cognitive functions (CANTAB® www.cantab.com). The regulatory accepted

digital tools have been utilised widely in drug development and clinical trials for cognitive research (but have not been used extensively for RRP research). Subjective measures and questionnaire data will be captured on the CANTAB electronic clinical outcome assessment (eCOA) platform.[20-22]

Study procedure overview

Screening will be overseen by Simbec-Orion site staff and will be conducted within 28 days of the first study session (for full screening procedures please refer to the study protocol, supplementary information). Eligible subjects will be asked to return for each of the 5 study sessions and be available for the post-study telephone call; continued eligibility will be re-confirmed at each session. Participants will attend the clinical unit the morning before the study session, staying at the unit overnight (there will be at least 7 days between the start times of each study session).

At study session 1 only, participants will be familiarised with the eCOA platform and asked to complete several baseline questionnaires. Participants will also complete the full CANTAB battery to allow familiarisation before use later in the study. At all sessions, whilst resident at the clinical unit, participants will be provided a standardised lunch, dinner and snack before initiating a smoking, nicotine, alcohol and caffeine abstinence for a minimum of 12 hours prior to commencement of the study session the following morning. Whilst in the unit, participants will refrain from strenuous exercise.

On the morning of the study session participants will be provided a standardised breakfast, consisting of a 250 ml orange juice, one yoghurt and one cereal bar (approximately 400 calories). The full breakfast is to be consumed within 15 minutes. Following a rest period of 115 minutes, participants will rate their alertness on the Karolinska sleepiness scale and emotion on the subjective emotion questionnaire and then complete the pre-product CANTAB assessment. Straight after, participants will then complete the Questionnaire on Smoking Urges - Brief and the Assessment of Caffeine Urges. After another rest period of a minimum of 30 minutes, participants will be given their assigned investigational product to use *ad libitum* for 5 minutes. Participants will then repeat the CANTAB assessment before again completing the subjective emotion questionnaire and Questionnaire on Smoking Urges - Brief. Finally, a product satisfaction questionnaire will be performed (unless no product is assigned) (Figure 1).

Devices will be weighed immediately before and after use to allow for calculation of device mass loss (DML). Light reading matter will be provided for participants during the rest periods but use of mobile phones or other personal electronic devices will not be permitted. Use of participants' own nicotine products will not be allowed until completion of the study session. Follow-up interviews will be performed by telephone 5-7 days after the final study session. Participants will be able to withdraw from the study at any time and for any reason. It will be possible to remove individual participants from the study if he or she experiences an intolerable adverse event (AE), fails to meet the inclusion and exclusion criteria or deviates from the study protocol at any time (at the discretion of the PI). The study will be discontinued if any unacceptable safety findings are identified. The decision will be made, provided in writing and signed by the PI (or deputy) and the sponsor and provided to the research ethics committee. The sponsor may also temporarily suspend or prematurely discontinue the study at any time due to safety or ethical issues or severe non-compliance.

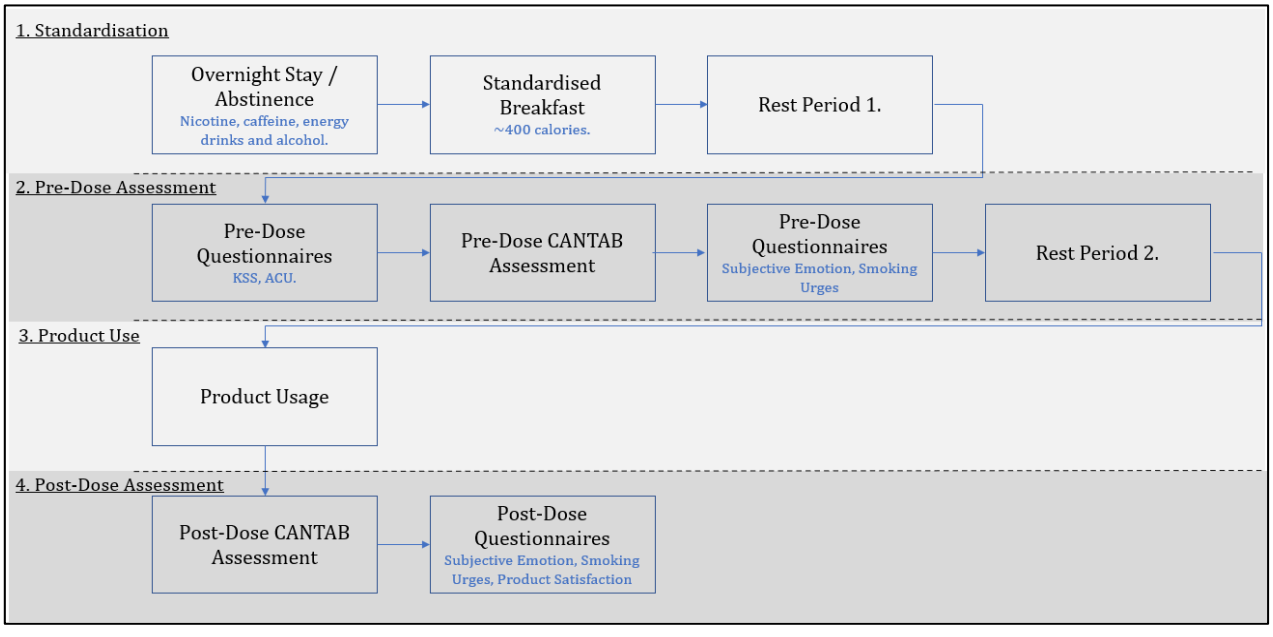

Figure 1: Study schematic.

Safety and data quality assurance

To assess safety, all AEs that occur during the entire study period will be graded according to severity and recorded in the case report forms along with the date of onset, likely relation of the AE to the investigational product, resolution and product use, action taken and outcome if known. AEs will be coded in the system organ classes and preferred terms of the medical dictionary for regulatory activities (MedDRA) version 24.1.

The study will be monitored by ORION Clinical Services Limited (Slough, UK). The monitor will make regular visits to the study site to check the completeness of master files and study records, accuracy of reporting on the case report forms and adherence to the protocol. Other checks will be progress of enrolment and storage, handling and accountability of the investigational products. Direct access to relevant anonymised clinical records to confirm their consistency with the data in the case report forms may be granted by the PI to the study monitor, auditor(s), research ethics committee and the UK Medicines and Healthcare Products Regulatory Agency. All study files and documentation will be archived for at least 25 years after the end of the study in line with the European medicine agency guideline INS/GCP/856758/2018.[17] Simbec-Orion will be responsible for maintaining participants' confidentiality.

Data captured in the case report forms will be provided to the Simbec-Orion statistics department as SAS datasets in a standard format that will be used for programming outputs. Questionnaire data will be sent by Cambridge Cognition to Simbec-Orion as an SAS dataset. The clinical database will be reviewed, all data issues resolved, the analysis sets approved and protocol deviation classifications agreed before database lock.

Statistical analysis

For the full statistical analysis approach, please refer to the SAP appended in the supplementary information.

Little information is available regarding variability and significant effect size in relation to the effect of nicotine on cognitive function. Significant effects have been observed in samples of 19 to 25 men assessed in randomised studies testing differences in scores before and after exposure per scoring period.[24-25] To allow for greater variability due to a broader age range and mix of sexes, it was estimated that a final sample size of 35 would be suitable to assess the endpoints; 40 participants will be recruited to account for ~10% attrition.

Analyses will be done on a per product basis in the per protocol population, which will include all participants who have at least one post-baseline cognitive assessment result and have adhered to the protocol. Data on product history and use during the study will be presented as numbers and percentages. Continuous variables will be presented as means with standard deviations and medians with ranges. Categorical variables will be reported with numbers and percentages.

Key outcome measures (highlighted in the SAP) for each of the CANTAB cognition tasks (RVP, SWM, OTS, PAL) will be reported with absolute and baseline-adjusted values summarised by product. Statistical comparisons will be performed between products by ANOVA or ANCOVA on the absolute and baseline-adjusted results. In addition to the individual key outcome measures, a global composite score across all key measures will be calculated (individual subject scores will be normalised by computing Z-scores). The global cognitive composite score for each subject will be derived as the mean Z-score across all key outcome measures; absolute and baseline adjusted global composite scores will again be compared between products by ANOVA.

Upon completion of the statistical analysis, additional ad hoc analysis may be justified that may inform future study designs in the field. All statistical analyses will be performed using SAS 9.4 or higher.

Expected results

Enrolment is complete and the study will be finalised by the time of publication. The results of this study are expected in 2022.

DISCUSSION

Published scientific evidence suggests that smoking can influence various physiological and psychological functions (including several subcomponents of cognitive function, namely sustained attention, working memory and executive function).[13] For some smokers, the loss of such effects have been cited as barriers to cigarette smoking cessation and the deficits in such effects may contribute to resumption of smoking post quitting.[16,17] The effect of e-cigarettes (and other reduced risk alternatives to cigarette smoking) on such functions has not been widely researched but may be important in the acceptability of e-cigarettes to existing smokers who would otherwise continue to smoke.

The hypothesis of this study is that acute nicotine delivery via an e-cigarette can influence attention, memory and executive function in current smokers following a period of smoking abstinence to the same extent as a combustible cigarette. As such, participants will be in a state of nicotine abstinence at the start of each session, known to contribute to cognitive function deficit and hence the results should be considered largely in the context of abstinence relief.[16,17] Such effects may be important in the acceptability of e-cigarettes to existing smokers. If the hypothesis is confirmed, the findings would provide support for the proposition that smokers seeking alternatives may find e-cigarettes a satisfactory

substitute for conventional cigarettes. A crossover design was chosen because it permits the assessment of differences within individuals (reducing data variability). The age range of 25-45 years is intended to minimise issues related to protocol adherence and other lifestyle factors. In older adults there is an increased risk of potentially confounding diseases and/or age-related physiological changes that may affect cognitive function.

Limitations

Although varied in their reported significance, cross-sectional studies generally demonstrate that there are multiple reported reasons why some people continue smoking despite the well known risks to health.[18-19] This exploratory, acute study focusses primarily on cognitive function (with an assessment of emotion and craving also) and hence doesn't account for all potential factors that may contribute to resumption of smoking post quitting. Furthermore, the study is an acute study (assessing cognitive function at only one time-point following product use (approximate product TMAX)) and hence longitudinal changes following sustained product switching are not assessed. Whilst utilised broadly in associated research fields, the research methodologies have also not been utilised extensively to assess RRPs. Additionally, study participants will be recruited from the UK population and consist of healthy smokers between the ages of 25-45. As such, the data may not be reflective of populations outside these ranges.

CONCLUSION

The potential physiological and psychological effects of e-cigarettes may play an important role in the acceptability of e-cigarettes to existing smokers; however, such effects have not been widely researched. In this vein, the purpose of this study is to build upon the growing general scientific knowledge about e-cigarettes, specifically trying to understand whether they may serve as a satisfactory substitute product for smokers seeking alternatives. The data will not be used to support any advertising or marketing purposes or to make any claims relating to cognitive function. The results will be submitted for publication in a peer-reviewed scientific journal irrespective of the study findings. We believe that this will be a high-quality study in the field of e-cigarette research and that the findings may add to the scientific knowledge on which informed and proportionate public health policy decisions can be based.

ACKNOWLEDGEMENTS

The authors would like to thank the efforts, expertise and professionalism of Simbec Orion (Merthyr Tydfil, UK) and Cambridge Cognition (Cambridge, UK) for their management and conduct of the clinical phase of the study. We are grateful for the assistance of James Ebajemito (BAT) and Anna Azzopardi (BAT) for their technical insight and contribution towards the study design.

Funding: British American Tobacco (Investments) Limited, Regents Park Road, Southampton, SO15 8TL, UK.
Conflict of interest: Harry Green, Olivia O'Shea and Nik Newland are current employees and stockholders of British American Tobacco (Investments) Ltd, which is the sponsor and funding source of this study. British American Tobacco (Investments) Ltd is the manufacturer and holder of the intellectual property rights of the investigational product used in this study.
Ethical approval: Ethical approval for the study has been obtained from Wales Research Ethics Committee 1 (Cardiff, UK; reference 21/WA/0095).

REFERENCES

1. WHO. WHO report on the global tobacco epidemic, 2021. Available at https://www.who.int/publications /i/item/9789240032095. Accessed on 02 October 2021.
2. World Population Review. Smoking rates by country, 2021. Available at: worldpopulationreview. com. Accessed on 10 December 2021.
3. Murphy J, Gaca M, Lowe F, Minet E, Breheny D, Prasad K, et al. Assessing modified risk tobacco and nicotine products: Description of the scientific framework and assessment of a closed modular electronic cigarette. Regulatory Toxicol Pharmacol. 2017;90:342-57.
4. Belushkin M, Djoko D, Esposito M, Korneliou A, Jeannet C, Lazzerini M, et al. Selected Harmful and Potentially Harmful Constituent Levels in Commercial E-Cigarettes. Chem Res Toxicol. 2020;33:657-68.
5. Margham J, McAdam K, Forster M, Liu C, Wright C, Mariner D, et al. Chemical composition of aerosol from an E-Cigarette: a quantitative comparison with cigarette smoke. Chem Res Toxicol. 2016;29:1662-78.
6. National Academies of Sciences, Engineering, and Medicine; Health and Medicine Division, Board on Population Health and Public Health Practice, Committee on the Review of the Health Effects of Electronic Nicotine Delivery Systems. Public Health Consequences of E-Cigarettes. Eaton DL, Kwan LY, Stratton K, eds. Washington, DC: National Academies Press (US); 2018.
7. McNeil A, Brose L, Calder S, Hajek P, McRobbie H. E-cigarettes: an advance update. A report commissioned by Public Health England. Am J Public Health. 2015;109(11):e26-7.
8. McNeill A, Brose L, Calder R, Erikas S, Robson D. Vaping in England: an evidence update including vaping for smoking cessation, 2021. Available at: Vaping in England: an evidence update including vaping for smoking cessation. Accessed on 10 December 2021.

9. Royal College of Physicians. Nicotine without smoke: tobacco harm reduction, 2016. Available at: https://www.rcplondon.ac.uk/projects/outputs/nicotine-without-smoke-tobacco-harm-reduction. Accessed on 10 December 2021.
10. McGovern J, Benowitz N. Cigarette smoking, nicotine, and body weight. Clin Pharmacol Ther. 2011;90:164-8.
11. Schwartz A, Bellissimo N. Nicotine and energy balance: A review examining the effect of nicotine on hormonal appetite regulation and energy expenditure. Appetite. 2021;164:105260.
12. Heishman S, Kleykamp B, Singleton E. Meta-analysis of the acute effect of nicotine and smoking on human performance. Psychopharmacol. 2011;210:453-69.
13. Benowitz N. Nicotine addiction. N Engl J Med. 2021;362:2295-303.
14. Borelli B, Mermelstein R. The role of weight concern and self-efficacy in smoking cessation and weight gain among smokers in a clinic-based cessation program. Addict Behav. 1998;23:609-22.
15. Jeffrey R, Hennrikus D, Lando H, Murray D, Liu J. Reconciling conflicting findings regarding postcessation weight concerns and success in smoking cessation. Health Psychol. 2000;19:242-6.
16. Ashare R, Falcone M, Lerman C. Cognitive Function During Nicotine Withdrawal: Implications for Nicotine Dependence Treatment. Neuropharmacol. 2014;76:581-91.
17. Hughes J. Effects of abstinence from tobacco: Valid symptoms and time course. Nic Tob Res. 2007;9:315-27.
18. Theobald W, Smith S, Fiore M. Insights: Smoking in Wisconsin University of Wisconsin Medical School: UW center for Tobacco Research and Intervention. 2002.
19. Guirguis A, Ray S, Zingone M, Airee A, Franks A, Keenum A. Smoking cessation: barriers to success and readiness to change. Tenn Med. 2010;103:45-9.
20. Barnett J, Blackwell A, Sahakian B, Robbins T. The paired associates learning (PAL) test: 30 years of CANTAB translational neuroscience from laboratory to bedside in dementia research. Curr Top Behav Neurosci. 2016;28:449-74.
21. Kaser M, Deakin J, Michael A, Zapata C, Bansal R, Ryan D et al. Modafinil improves episodic memory and working memory cognition in patients with remitted depression: A double-blind, randomised, placebo-controlled study. Biological Psychiatry. 2017;2:115-22.
22. AhnAllen C, Bidwell L, Tidey J. Cognitive effects of very low nicotine content cigarettes, with and without nicotine replacement, in smokers with schizophrenia and controls. Nicotine Tobacco Res. 2014;17:510-14.
23. Ebajemito J, McEwan M, Gale N, Camacho O, Hardie G, Proctor C. A randomised controlled single-centre open-label pharmacokinetic study to examine various approaches of nicotine delivery using electronic cigarettes. Sci Rep. 2020;10:19980.
24. Wesnes K, Warburton D. The effects of cigarettes of varying yield on rapid information processing performance. Psychopharmacol. 1984;82:338-42.
25. Edwards J, Wesnes K, Warburton D, Gale A. Evidence of more rapid stimulus evaluation following cigarette smoking. Addict Behav. 1985;10:113-26.

Cite this article as: Green HJ, O'shea OK, Philpott HL, Newland N. An exploratory, randomised, crossover study to investigate the effect of nicotine on cognitive function in healthy adult smokers who use an electronic cigarette, after a period of smoking abstinence: study protocol. Int J Clin Trials 2022;9(2):136-42.