International randomised controlled trial evaluating metabolic syndrome in type 2 diabetic cigarette smokers following switching to combustion-free nicotine delivery systems: the DIASMOKE protocol

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ABSTRACT

Introduction Reducing exposure to cigarette smoke is an imperative for public health and for patients with diabetes. Increasingly, combustion-free nicotine delivery systems (C-F NDS) such as e-cigarettes and heated tobacco products are substituting conventional cigarette use, and accelerating the downward trends in smoking prevalence. However, there is limited information about the long-term health impact in patients with diabetes who use C-F NDS. This randomised trial of type 2 diabetic cigarette smokers will test the hypothesis that following a switch from conventional cigarettes to C-F NDS, measurable improvement in metabolic syndrome (MetS) factors will be shown over the course of 2 years.

Methods and analysis This study is multicentre and will take place in five locations in four countries in an armoured setting. A total of 576 patients with diabetes will be randomised (1:2 ratio) to either a control arm (Study Arm A), in which they will be offered referral to smoking cessation programmes, or to an intervention arm (Study Arm B) assigned to C-F NDS use. Participants will be at least 23 years old and of any gender. Patient recruitment will start in February 2021 and is expected to be completed by December 2021. Primary outcome measures include fasting plasma glucose, blood pressure, triglycerides, high density lipoprotein and waist circumference, while secondary feature absolute change in the sum of the individual factors of MetS and change in each individual factor of MetS measured at each study time point.

Ethics and dissemination The approval of research ethics committee (REC) regarding the trial protocol, informed consent forms and other relevant documents is required to commence the study. Substantial amendments to the study protocol cannot be implemented until the REC grants a favourable opinion. The results of the study are intended to be published as articles in high quality peer-reviewed journals and disseminated through conference papers.

Strengths and limitations of this study

DIASMOKE will be the first study to determine an overall health impact of combustion-free nicotine delivery systems (C-F NDS) in diabetes and its cardiovascular risk.

Adherence to C-F NDS will be strengthened by providing a wide variety of different products to meet patients’ preference.

Compliance to the study protocol will be monitored daily via a mobile application.

Due to the relatively long duration of the study, adequate participants’ retention may be challenging.

Study results cannot be generalised to people with type 1 diabetes mellitus (T1DM) or with unstable T2DM.

Trial registration number NCT04231838. Pre-results stage.

BACKGROUND

Diabetes mellitus (DM) can cause irreversible damage to the blood vessels leading to microvascular (retinopathy, nephropathy and diabetic neuropathy) or macrovascular (coronary artery disease, stroke, peripheral arterial disease) complications, the latter cardiovascular complications being most common, and a frequent cause of death. Besides diabetes and hyperglycaemia, obesity, hypertension and dyslipidaemia are well established cardiovascular risk factors, all of which come under the umbrella definition of metabolic syndrome. Other cardiovascular
risk factors may also coexist in these patients, the most important being smoking.

Cigarette smoking is a strong cardiovascular risk factor not included in the definition of metabolic syndrome (MetS) but substantially increases the risk of microvascular and macrovascular complications in patients with type 2 DM (T2DM)\(^\text{2,24}\) whereas quitting smoking substantially reduces this risk.\(^\text{4-7}\) Given that exposure to cigarette smoke is associated with vascular damage, endothelial dysfunction and activation of coagulation and fibrinolysis,\(^\text{8-10}\) it is not surprising that smoking enhances the combined harmful effects of elevated blood glucose and other risk factors and accelerates vascular damage in patients with diabetes.

If reducing exposure to cigarette smoke is an imperative for public health, it is even more so for patients with T2DM.\(^\text{11}\) However, prevalence of smoking among people with DM appears to be similar to that of the general population.\(^\text{12}\) In the USA, the prevalence of tobacco consumption has decreased substantially, but this beneficial trend has not been observed in patients with DM.\(^\text{13}\)

There is a clear urgent need to target patients with T2DM to successful smoking cessation therapies, such as nicotine-containing preparations.\(^\text{14,15}\) Unfortunately, there is no convincing demonstration of effective cessation interventions in patients with diabetes\(^\text{16}\) and, in general, most smokers are reluctant to seek formal assistance for stopping smoking with the vast majority making attempts to quit without assistance.\(^\text{17,18}\) Consequently, the need for novel and more efficient approaches is required.

Combustion-free technologies for nicotine delivery such as e-cigarettes (ECs) and heated tobacco products (HTPs) are substituting conventional cigarettes globally\(^\text{19}\) and are thought to be less harmful alternative to tobacco smoking.\(^\text{20-22}\) However, there are no long-term studies assessing cardiovascular risk or effect of cardiovascular risk factors in patients with diabetes who use these technologies.

The DIASMOKE collaborators seek to determine whether T2DM cigarette smokers who switch to combustion-free nicotine delivery systems (CF NDS) experience measurable improvements in their cardiovascular risk parameters.

### Methods

**DIASMOKE** (Assessing the impact of combustion-free nicotine delivery technologies in DIAbetic SMOKers) is an international, multicentre, open-label, randomised controlled study analysing two parallel groups of participants, designed to determine whether T2DM cigarette smokers switching to CF NDS experience measurable improvement in cardiovascular risk parameters as a consequence of avoiding exposure to cigarette smoke toxics.

### Study population

The inclusion and exclusion criteria are summarised in **box 1**. Participants will be recruited from a group of cigarette smokers with a clinical diagnosis of T2DM. Only regular cigarette smokers will be considered for inclusion (criteria mentioned in **box 1**). Smoking status will be verified by an exhaled carbon monoxide (CO) measurement (exhaled CO ≥7 ppm) at the screening visit. Each participant will be offered access to local free smoking cessation programmes, and only those who refuse participation in cessation programmes and are willing to switch to a CF NDS will be randomised following informed consent. Participants included will be willing to refrain from eating/drinking prior to the screening visit and check-in at each study visit.

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**Box 1 Inclusion and exclusion criteria**

**Inclusion criteria**

- Written, informed consent signed before any study-specific procedure.
- Men or women aged 23 years and older.
- Regular smokers of at least 10 cigarettes/day (maximum of 30 cigarettes/day) for at least 5 consecutive years prior to the screening visit.
- Type 2 diabetes mellitus (as defined by the American Diabetes Association).
- 6.5%<glycated haemoglobin<10%.
- Body mass index between 18.5 kg/m² and 34.9 kg/m², both inclusive.
- Body weight exceeding at least 50 kg (men) or 40 kg (women).
- Exhaled carbon monoxide level of at least 7 ppm (parts per million).

**Exclusion criteria**

- History of recent acute decompensation of their disease requiring treatment within 4 weeks prior to visit.
- Known clinically-significant neurological, gastrointestinal, renal, hepatic, cardiovascular, psychiatric, respiratory, metabolic, endocrine, haematological or other disorder that, in the opinion of the investigator or their appropriately qualified designee, would jeopardise the safety of the participant or impact on the validity of the study results.
- Any other condition or therapy that would make the patient unsuitable for the studies and will not allow participation for the full planned study period (eg, active malignancy or other condition limiting life expectancy to <12 months).
- A significant history of alcoholism or drug/chemical abuse within 24 months prior to screening.
- Regular use of any nicotine or tobacco product other than their own cigarettes within 14 days of screening.
- Pregnant or breast feeding or intention to become pregnant during the studies.
- Previous (within 90 days prior to randomisation) or concomitant participation in another clinical study involving administration of an investigational drug.
- Close affiliation with the investigational site; for example, a close relative of the investigator, dependent person (eg, employee or student of the investigational site).

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Open access
Study design

The study design flow of DIASMOKE is illustrated in figure 1. The project will take place in five locations in four different countries (UK, Italy, Poland and Moldova) in an ambulatory setting.

Participants will attend a screening visit within 28 days prior to visit 1 (table 1A) and undergo demographic assessments including socio-demographic data, detailed medical history (including medication use), detailed smoking, vaping and eTPs use history and their intention to quit. Modification in their diet and/or anti-diabetic medication will be recorded regularly throughout the study. All patients will be offered smoking cessation programme as per local guidelines. Participants will be offered a further second opportunity to enrol in the free local smoking cessation programme prior to enrolment.

Following baseline assessments on day 1 (table 1B), participants will be randomised to either the control (A) arm or the intervention (B) arm. The randomisation sequence will be computer generated, with an allocation ratio of 1:2 (arm A:arm B) in order to compensate for the estimated 50% drop-out rate. The patient will be allocated to one of the study arms automatically after the staff will access the web-based application entering their participant identification number, a month and a year of birth and initials into the programme. Patients randomised into arm B will be allowed to choose the product of their preference from the given pool of the popular C-F NDS. The participants will be trained and counselled on the chosen device and given a full 1-week supply of tobacco sticks/EC cartridges/e-liquids refill bottles prior to check-out on day 1. After randomisation, a dedicated tracker application will be installed on patients’ smartphones. The application is designed to track patients’ behaviour (physical activity, adherence to sugar testing, cigarette smoking frequency, C-F NDS usage) to identify protocol violations that will generate flagging events and alerts to collect adverse events and to send reminders (next scheduled appointment, study restrictions, instructions and so on) throughout the whole duration of the study.

Subsequently, participants will be invited to attend four further clinical visits conducted in an ambulatory setting (visits 2–5) to undergo a range of measurements and blood tests (table 1A). Following each visit participants will be supplied with an appropriate amount of consumables (tobacco sticks, EC cartridges, e-liquid refill bottles). Participants will fast overnight (from midnight) prior to each visit and will undergo clinical laboratory evaluations which will be performed. Patients will be instructed to refrain from consuming alcohol for 24 hours prior to clinic visits and instructed not to consume more than 14 units of alcohol per week for the entire duration of the study.

For patients randomised into arm B, between those clinical visits, additional non-clinical visits aiming to replace the used consumables are planned. At non-clinical visits, study investigators will also have the opportunity to stimulate retention and check compliance. In order to perform an evaluation of the habitual pattern of use of the C-F NDS and to verify product adherence, patients randomised into arm B will return all empty, part-used and unused consumables at each visit.

At each visit, all participants will be advised and encouraged to completely quit smoking (cigarette or C-F NDS). They will explicitly be told about the risks associated with smoking and at every contact time point, referred to local free smoking cessation programmes.

Premature withdrawal from the study may occur if a participant: (1) experiences a severe adverse event (SAE); (2) sustains any protocol violations; (3) uncooperates during the conduct of the study, which cannot be corrected; (3) is uncooperative, including non-attendance; (4) decides to stop his/her participation at any moment of the study; (5) becomes pregnant. DIASMOKE is an unblinded study due to its specifications.

It is not possible to blind participants to the intervention they will be receiving as well as trial staff when providing the interventions and collecting data. Source data and source documents will be managed according to the Good Clinical Practice guidelines.

The trial will formally end on the date of the last visit of the last patient in the last country undertaking the trial. In order to provide an adequate data collection each in every country, patients will be allocated a case report form (CRF). CRF will be an electronic document. The data will be used to perform statistical analysis for the trial. Anonymised data from each study visit will be entered directly onto the CRF as it will then become a source document. The CRFs will be web-based and all study sites will have access to their information. In order to promote data quality the study will use standardised instruments such as Diabetes Quality of Life questionnaire or Fagerström Test For Nicotine Dependence. Personal data will be protected as each participant will be allocated a unique study identification number (patient ID). Participants’ personal details will not be attached to the research results and the decoding list will only be available to a limited number of members of the research team. All information obtained during the study procedures will be treated as private and confidential.

Patient and public involvement

A focus group of smokers with diabetes was organised on 25 February 2020 and feedback from smokers was used in the trial design. Further, the study has been reviewed by Ashford and St Peter’s Hospitals NHS Foundation Trust’s Research and Development Committee, which includes a patient representative.

Objectives and endpoints

The primary objective of DIASMOKE is to assess the impact of sustained use of C-F NDS on the proportion of patients with metabolic syndrome, as defined by National Cholesterol Education Program (NCEP) MetS score below the diagnostic threshold (<3). The primary
Figure 1  Study design of DIASMOKE. Flow chart summarising the study design. Initial screening visit will be followed by visit 1, during which participants will be randomised to one of the study arms (Arm A and Arm B). Patients in both arms will be invited to attend further clinical visits (V2–V5). All participants will be given an opportunity to enrol in the free local smoking cessation programme at each visit. C-FNDS, combustion-free nicotine delivery systems; T2DM, type 2 diabetes mellitus.
The main prespecified secondary endpoint is an absolute change in the sum of the individual factors of the MetS (as defined by NCEP criteria) measured at each study time point (between and within study groups). Other secondary endpoints include change in each individual factor of the MetS (as defined by NCEP criteria) measured at each study time point (between and within study groups) and change of the variables given in table 1B measured at each study time point (between and within study groups).

**Statistical considerations**

**Powering and sample size calculation**

For this study, the following input assumptions were considered:

- The absolute reduction in MetS prevalence following substantial smoking cessation is expected to be 15%, based on the results of a range of lifestyle modification interventions.24–28
- The baseline prevalence of MetS in T2DM is expected to be 70%.29–32

The sample size was calculated on the basis of demonstration of superiority, using an assumption of normal distribution, as described by Pocock.33 Significance level was set at 5% (α=0.05), with a power of 80% (β=0.20). On this basis, the minimum number of patients with analysable data required is 160 per treatment arm (N).

Further assumptions at the planning stage included an estimated 50% proportion of patients randomised to C-F NDS who are expected to achieve sustained reduction in cigarette consumption of at least 80% for the duration of the study (%SusRed).34–38

The adjusted number of patients in the intervention arm (N₁) was therefore increased to 320:

$$N₁ = N \times \frac{\% \text{SusRed}}{320} = 320 \times \frac{50}{100} = 160 \times \frac{50}{100}$$

Additionally, the expected number of patients in both arms withdrawing from the trial over 2 years is estimated at 20%.39–41 The total number of patients recruited to each treatment arm was therefore increased by this amount:

- Intervention arm: 320×1.2=384.
- Control arm: 160×1.2=192.
- Total patients both arms=576.

In order to reach the target sample size patients with diabetes will be informed about the potential benefits of switching to C-F NDS as well as the ability to report their health problems to their site investigator via a mobile application.

**Statistical analyses**

The primary endpoint for the statistical analysis is defined as the between-groups difference in calculated prevalence of MetS after at least 24 months of follow-up. The full analysis set (FAS) comprises all patients randomised to the intervention arm who achieve a sustained reduction in cigarette consumption of at least 80% across the study period for at least 50% of the study period, with comparison being made between groups difference in calculated prevalence being made between patients with T2DM randomised to each arm of the study.
full duration of follow-up combined with all patients randomised into the standard care control group.

The FAS will be the primary analysis set for all efficacy analysis. Two approaches to the primary analysis will be used: (a) Unadjusted analysis, based on a direct comparison of the change in prevalence. Z test will be used to assess the significance of difference between the two groups in the prevalence percentage changes from baseline to 24-month visit. (b) Adjusted analysis. Baseline demographics, clinical and concomitant therapeutic characteristics will be analysed to identify potential confounders for the primary outcome that are unbalanced between treatment groups. The primary outcome will then be re-analysed using a generalised linear model adjusting for all identified confounders.

Any difference between groups will be assessed for statistical significance at a two-sided alpha of 0.05.

Monitoring
An independent data monitoring and safety committee (DMC) will be established for this study before the first participant is randomised and will overview the safety of the study. The DMC will review safety data on a periodic basis, and make recommendations to continue, modify or stop the study. The DMC will evaluate and perform efficacy analysis. The primary outcome after 6 months or otherwise if determined by the committee and make a recommendation regarding early termination based on the observed results of the study on grounds of an unfavourable risk-benefit profile. In the event that the assumptions underlying the sample size calculation are seen to be incorrect at the time of the interim analysis, they will have the option to advise further recruitment to the study, without disclosing the interim results to the study investigators. The DMC will be independent from the sponsor and competing interests.

A trial monitoring plan will be developed and agreed by the trial steering committee (TSC) and chief investigator, based on the trial risk assessment which may include on-site monitoring. The contact research organisation (Metanoic Health Ltd) will arrange and monitor data entry and data quality assurance from investigators and the sponsor. The processes reviewed can relate to participant recruitment, consent, eligibility and allocation to trial arms, adherence to trial interventions and policies to protect participants, including reporting of harms, completeness, accuracy and timeliness of data collection. Monitoring will be done by exploring the trial data set on performing site visits.

Any adverse event (AE) and serious adverse event (SAE) will be noted during the whole duration of the study. AEs and SAEs will be recorded on baseline and at each subsequent study visit in the adverse event page of the CRF. Signs or symptoms will be investigated at each visit by interviewing the participants. Patients will also be encouraged to report AEs/SAEs at any time during the study. The investigator must pursue and obtain information adequate both to determine the outcome of the AE and to assess whether it meets the criteria for classification as a SAE requiring immediate notification to the competent authority. Sufficient information should be obtained to assess causality. Follow-up of the AE/SAE after the date of study discontinuation is required if the AE/SAE or its sequelae persist.

Ethics and dissemination
The study will be conducted according to the principles of Good Clinical Practice and Declaration of Helsinki. All five local ethics committees reviewed and approved the study and—where appropriate—translated relevant documentation (informed consent form, patient information sheet and so on). A list of the ethics committees that reviewed and approved the study is available as online supplemental file 1. Any amendments to this protocol are required the chief investigator will be responsible for the decision to amend the protocol and for deciding whether an amendment is substantial or non-substantial. Any substantial amendments will be submitted to the research ethics committee for approval before implementation. Any amendments will apply to all sites.

The informed consent or assent from potential trial participants will be obtained by site investigators through relevant forms (see online supplemental file 2).

In the UK all investigators and trial site staff will comply with the requirements of the Data Protection Act 2018, with regards to the collection, storage, processing and disclosure of personal information and will uphold the Act’s core principles. In other countries any equivalent data protection regulations will be complied with.

The trial steering committee (TSC) will have access to the full trial data set. A formal access request from site investigator(s) will require TSC and sponsor approval. All committee members are independent and have no conflict of interest.

The intention of the TSC is to disseminate the results of the study through journal articles in high quality peer-reviewed journals and through conference papers. A summary of results will be available on the Ashford and St Peter’s Hospitals website where patients and members of the public will be able to access it. The sponsor institution has open data access policy and the anonymised data will be available on request to any researcher following approval from the established scientific committee.

The informed consent materials (consent form and patient information sheet) are attached as online supplemental files 2 and 3.

RESULTS
Patient recruitment will start in February 2021 and enrolment is expected to be completed by December 2021. Results will be reported between 2023 and 2024.

DISCUSSION
Little is known about the impact of C-F NDS on patients with T2DM who smoke. Products that do not require combustion to deliver nicotine, such as ECs and HTPs
are substituting conventional cigarettes globally. They potentially offer substantial reduction in exposure to harmful and potentially harmful chemical constituents compared with conventional cigarettes. DIASMOKE will be the first study determining the overall health impact of using such technologies in patients with diabetes. Undoubtedly, it is desirable for patients to avoid consumption of any tobacco-related inhalation products, but in order for governments, health authorities (e.g. European Medicines Agency, Food and Drug Administration) and clinicians to provide guidance about cigarette substitution, robust evidence-based information is required.

We designed this international randomised controlled trial (RCT) to gather such evidence. In particular, we will be testing the hypothesis that avoiding exposure to cigarette smoke toxicants may translate to measurable improvement in cardiovascular risk factors when patients with T2DM who smoke switch to using C-F NDS compared with patients with T2DM who continue to smoke conventional cigarettes. Several parameters measured in this study are associated with the development of cardiovascular diseases (such as high blood pressure, elevated blood cholesterol and BMI >25) and some of these indicators have been shown to improve relatively soon after smoking cessation. Consequendy, the profile of these changes after switching to C-F NDS could provide valuable insights into the overall potential of C-F NDS to reduce the risk of cardiovascular disease.

The decision for a switching study design in DIASMOKE has been guided by the notion that C-F NDS have been promoted as substitutes for tobacco cigarettes. In a switching study of smokers the reference product is their own brand tobacco cigarette. The length of the study was based on the consideration that changes in the primary endpoint could be reasonably observed as early as 6 months. It is however possible that a much longer follow-up period could be necessary to firmly establish findings consistency over time, since study duration was extended to 24 months. The RCT study design will provide a robust answer to determine the health impact of C-F NDS use on patients with diabetes. Clearly, randomisation will equalise variation in smoking history and other variables between study arms, thus ensuring high quality data. Importantly, the entire study is designed keeping the welfare of all participants at its centre; at every contact smokers will be asked to stop all types of smoking and provided with free local referrals for smoking cessation programmes.

Compliance to the study protocol is critical as failure to fully or largely replace conventional cigarettes with C-F NDS would reduce or nullify the expected changes in study endpoints. Participants will be reminded on the importance of adhering to their randomised product allocation and of abstaining from or greatly reducing conventional cigarette consumption (by at least 80% from their baseline value of cigarette smoked in a day) at every contact. They will also be informed that biochemical verification of compliance as well as assessments of adherence will be conducted at each clinic visit. In addition, any non-compliance will be recorded in the study diary after counting all empty, part-used and unused consumables returned at each visit, and tracked by the application. Although not expected that compliance for this study will be materially different compared with other comparable studies, our power calculations were overestimated to take account of a non-compliance rate of 50%. Thus, the C-F NDS population will be oversampled by adopting a 1:2 randomisation ratio scheme (ie, every patient randomised in the control population will be randomised in the C-F NDS population). Lastly, trial attendance and retention of the C-F NDS population will also be improved by asking participants to return to the clinic for their regular supply of tobacco sticks/e-cigarettes/e-liquids refillables.

This study has several innovative features. To improve adherence to C-F NDS (and maximise overall compliance to the study protocol), patients randomised to switching to C-F NDS will be offered a wide selection of different products (reflecting the most popular of those commercially available in each participating country) in order to choose the C-F NDS of their preference. Given that the population sample in DIASMOKE is mostly made of elderly patients, we will only offer devices that guarantee a likely user-friendly experience (ie, easy to refill consumables, prefilled consumables and heated tobacco devices). We expect that when participants are freely provided C-F NDS of their choosing they will be more likely to adopt the new technology and switch away from their own conventional cigarettes. Moreover, the study findings will not be product specific and unlikely to be limited in generalisability.

Our study has limitations. First, due to the relatively long duration of the study (24 months), maintaining a sufficient level of subject retention may be a challenge. Nonetheless, trial attendance and retention is likely improved by inviting participants to return to the clinic for their free supply of study products and by offering a dedicated fast track approach for their outpatient clinic appointments. Second, DIASMOKE results cannot be generalised to all patients with diabetes who smoke. We will recruit a (ambulatory) population of diabetic smokers who have been stably treated for T2DM. Therefore, the study protocol excludes smokers with untreated disease and T1DM smokers. Last but not least, COVID-19 restrictions may slow down recruitment in some countries. A competitive recruitment strategy and staggered activation of clinical sites less impacted by the pandemic, will be implemented to minimise the possible negative effect. Substantiation of the reduced risk potential of long-term C-F NDS use is virtually unexplored. Data from DIASMOKE will be an important addition to the growing body of evidence in the field of understanding the health impact of combustion-free nicotine delivery technologies...
and will provide valuable insights into the overall potential of these products to reduce the risk of cardiovascular disease in individuals, particularly patients with diabetes.

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**Contributors**
The Steering Committee will take responsibility for the scientific validity of the study protocol, assessment of study quality and conduct as well as for the scientific quality of the final study report. All Committee members are independent of the funder and have no conflicts of interest. Committee members will be: Prof Pankaj Sharma, Chief Investigator, UK; Chair; Dr Chong Lim, Principal Investigator, UK; Prof Edward Franek, Principal Investigator, Poland; Deputy Chair; Dr Prof Francesco Purrello, Principal Investigator (Site 1), Italy; Prof Maria Di Mauro, Principal Investigator (Site 2), Italy; Prof Lorina Vuletic, Principal Investigator, Moldova; Prof Farrukh Igbal; Dr David Crook, Research Delivery Service, University of Brighton, UK; Data Monitoring & Safety Committee (see page 10 of the manuscript). Dr Jonathan Belsey, JB Medical (UK); Prof Aldo Calogero, Italy; Prof Francesco Battista (Italy); Dr David Fluck (UK).

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The ethics committees that reviewed and approved the study

1. London - Hampstead Research Ethics Committee
   Manchester, UK
   20/LO/0704

2. Catania 1 Ethics Committee
   Catania, Italy
   164/2020/PO

3. Catania 2 Ethics Committee
   Catania, Italy
   71/2020/CECT2

4. Komisja Etyki i Nadzoru nad Badaniami na Ludziach i Zwierzętach przy CSK MSWiA w Warszawie
   Warsaw, Poland
   34/2020

5. National Committee for Ethical Expertise of Clinical Trial
   Chisinau, Moldova
   CNEESC/870/01.06.2020
CONSENT FORM

Full Study title: A Randomised Controlled International Multicentre Study evaluating changes in Metabolic Syndrome in Smokers with type 2 Diabetes Mellitus after switching from Tobacco Cigarettes to Combustion-Free Nicotine Delivery Systems: DIASMOKE Study.

Study Acronym: DIASMOKE

Short Study Title: Metabolic Syndrome in Diabetic Smokers using Cigarettes & Combustion-Free Nicotine Delivery Systems

Name of PI: Dr Chong Lim

Patient Identification Number: ____________

1. I confirm that I have read and understood the Patient Information Sheet dated 23rd May 2020, UK Version 2.1. I have had the opportunity to consider the information given concerning this study and to ask questions and have had these answered satisfactorily.

2. I confirm that I have been offered to join Trust smoking cessation programme which I have declined.

3. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving a reason. My legal rights and medical care will not be affected by my decision.

4. I understand that relevant sections of my medical notes and data collected during the study, may be looked at by individuals from the research team, from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I agree that my data collected for the study will be recorded anonymously and forwarded to the company ECLAT srl for evaluation.

5. I agree to my personal data being stored for a period of 6-12 months after the end of the clinical investigation. After this my data will be deleted. However, my study related anonymised data can be used for analysis and publications for 5 years after the end of the study.

6. I agree to take part in this study and also agree that you inform my GP about my participation in this study.

| Name of participant | Date | Signature |
|---------------------|------|-----------|
|                     |      |           |

| Name of person taking consent (If different from Researcher) | Date | Signature |
|------------------------------------------------------------|------|-----------|
|                                                            |      |           |

| Researcher | Date | Signature |
|------------|------|-----------|
|            |      |           |

1 copy for patient; Original for researcher; 1 copy to be kept with hospital notes

DIASMOKE Study- IRAS Project ID: 280909, Consent Form Version 2.1, 23 May 2020
Patient Information Sheet

Full Study title: A Randomised Controlled International Multicentre Study evaluating changes in Metabolic Syndrome in Smokers with type 2 Diabetes Mellitus after switching from Tobacco Cigarettes to Combustion-Free Nicotine Delivery Systems: DIASMOKE Study.

Study Acronym: DIASMOKE

Short Study Title: Metabolic Syndrome in Diabetic Smokers using Cigarettes & Combustion-Free Nicotine Delivery Systems

Dear Patient,

We would like to ask you to take part in our clinical investigation study. Before you decide whether you would like to take part it is important that you understand why this research is being done and what it will involve. One of our team will go through this information sheet with you and answer any questions or concerns you may have. Please ask us if there is anything that is not clear or if you would like more information and talk to others if you wish. You may take as much time as you wish before you decide whether you would like to take part in this study.

This information sheet will explain the purpose of the study and what will happen to you if you take part.

Thank you for taking the time to read this document.

What is the purpose of the study?
This study investigates whether vaping or using E-cigarettes reduces the risk of cardiovascular (heart and circulation) disease as compared to normal smoking. The results of the study may help us to understand more about the risks of vaping or e-cigarettes and normal cigarettes for diabetes patients who are smokers.

Why have I been chosen?
You will be invited to participate in this study if you are smoker and have diabetes and you have certain characteristics that have been set for the study.

Do I have to take part?
Your participation in this study is completely voluntary. You do not have to take part and you do not have to make your decision immediately. Please take the time to read this information sheet carefully and discuss it with relatives, friends and your GP if you wish.

It is up to you to decide whether or not to take part in this study. If you do decide to take part, you will be given this information sheet to keep and be asked to sign a consent form. You will

DIASMOKE Study- IRAS Project ID: 280909, PIS Version 2.1, 23 May 2020
be free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care you receive.

If you have any questions or concerns about this study, or if you do not fully understand any part of it, please ask the researchers (there are contact details at the end of this sheet).

**What will happen if I take part?**

If you are interested in taking part in this study, we will make sure that you understand the purpose of the study, and what taking part involves for you; also to answer any questions that you have. If you are happy to go ahead you will be invited to a baseline check around one month after your initial discussion about the study, and we will ask you to sign a consent form.

The study will last for around 2 years in total. After your baseline check, you will be asked to come back for four further checks after 3 months, 6 months, one year and two years.

Everyone who joins the study will be randomly chosen to be in one of two groups of participants. One group will be asked to carry on smoking their usual cigarettes for the duration of the study, and the second group will be asked to switch to vaping or using E-cigarettes (technically known as a ‘non-combustible nicotine delivery system’) instead of normal cigarettes. You will be asked to keep to the method chosen for the group you are in for as long as you are in the study.

At your baseline check we will take a ‘fasting blood sample’ so you will be asked not to eat or drink anything overnight before the appointment. During the visit we will ask some details about your medical history and your smoking, take some measurements and give you a short questionnaire. Finally, we will install an app on your phone to track some aspects of your lifestyle between visits.

If you are in the group using vaping or E-cigarettes, we will show you different devices you can use, so that you can chose what works best for you. We will explain how to use them, and provide you with tobacco sticks or e-liquids appropriate for your device throughout the study.

At the later visits (at 3 months, 6 months, one year and two years), you will be given a morning appointment, and asked to fast overnight before the visit. You will have a similar set of questions, tests and measurements to the baseline check. If you are in the group using vaping/E-cigarettes we will ask about how you have been getting on with these.

**What types of test or analysis will be carried out on the samples and what will happen to any samples I give?**

The study will include collection of Blood samples and Urine Samples from you.
Blood samples will measure: CBC (WBC Hb, platelets), lipid profile (Triglycerides, LDL and HDL cholesterol) HbA1C, Insulin level, Testosterone (men only) and, Urine samples will measure Urine Albumin Creatinine Ratio.

Only the Direct Clinical & Research Team at the NHS Trust will collect these samples.

All samples will be stored in a secure facility in an anonymised form at St Peters Hospital and sent to the Pathology department for analysis. Only the research team will have access to the samples.

If you withdraw your consent from participating further in the study after samples have been taken from you, your samples will be destroyed in accordance with the Human Tissue Authority’s Code of Practice and no new data will be generated from your samples. However, existing data cannot be removed.

**Will expenses be paid?**

If you have to make a special trip to the hospital as a result of taking part of this study, when you do not have a routine hospital appointment, we will be able to reimburse your travel expenses.

**What are the possible benefits of taking part?**

There may be no direct benefit to you from the study, apart from closer monitoring and medical supervision than would usually be available through standard NHS care. **All participants can stop using cigarettes at any point in the study and this is the preferred option from a health point of view.** However, your participation will be important as it will help us understand more about the effects of smoking and vaping or E-cigarettes, and this may help us to improve recommendations and treatments for people with diabetes in the future.

If you are chosen to be in the group trying vaping or E-cigarettes you will have a chance to try a different product instead of cigarettes.

**What are the possible disadvantages and risks of taking part?**

This will depend on which group you are allocated to in the study. If you are chosen to continue with your usual cigarettes, there will be no additional risks or disadvantages to taking part in the study. However, risks posed by smoking such as respiratory/cardiovascular will continue to increase with time. If you are chosen to try vaping or E-cigarettes, it is possible that you might have a reaction to the products. We will be monitoring this very carefully, and will ensure that if you have any problems they will be dealt with immediately. If necessary, you would be withdrawn from the study. You will have access to trial physician on priority basis to deal with any risk or adverse event.
We do not expect there to be any risks from the tests and assessments we will be carrying out, and trained staff will be supervising you at all times. If you have any problems they will be able to stop the test if necessary.

Whichever group you are allocated to, your normal care and treatment will continue unaffected.

**What if there is a problem?**

If you have a concern about any aspect of this study, you should ask to speak to the researchers who will do their best to answer your questions. If you remain unhappy and wish to complain formally, you can do this by contacting our hospital. Should you require advice in making your complaint, officers from the [Insert local hospital details] Patient Advice and Liaison Service (PALS) at St Peter’s Hospital will be able to help you. Their contact details are:

Telephone: 01932 723553
Email: Asp-tr.patient.advice@nhs.net

**What if something goes wrong? What arrangements are in place to cover me in terms of compensation?**

Indemnification for non-negligent harm will be provided by the sponsor in full accordance with the Association of the British Pharmaceutical Industry (ABPI) guidance. The sponsor company holds an insurance policy providing Primary No Fault Compensation Clinical Trials Insurance to compensate you from any harm arising due to the design and management of this research. The NHS indemnity is also in place which will cover you in case any harm arises during the conduct of this research.

**What will happen if I decide to withdraw at any point?**

You are free to withdraw your participation at any time without any effect on your standard of care. We will need to use the data collected on you up until the time of your withdrawal.

**Will my taking part in this study be kept confidential?**

Yes. We will follow ethical and legal practice and all information about you will be handled in confidence.

**How will we use information about you?**

We will need to use information from you and from your medical records for this research project. This information will include your name, contact details and NHS number. People will use this information to do the research or to check your records to make sure that the research is being done properly.
People who do not need to know who you are will not be able to see your name or contact details. Your data will have a code number instead.

We will keep all information about you safe and secure.

Once we have finished the study, we will keep some of the data so we can check the results. We will write our reports in a way that no-one can work out that you took part in the study.

**What are your choices about how your information is used?**

- You can stop being part of the study at any time, without giving a reason, but we will keep information about you that we already have.
- We need to manage your records in specific ways for the research to be reliable. This means that we won’t be able to let you see or change the data we hold about you.

**Where can you find out more about how your information is used?**

You can find out more about how we use your information:

- At [www.hra.nhs.uk/information-about-patients/](http://www.hra.nhs.uk/information-about-patients/)
- our leaflet available from the research team
- by asking one of the research team
- by sending an email to: asp-tr.rd-research-and-development@nhs.net

**How long will my personal data be stored or accessed after the study has ended?**

Your personal data will be stored or accessed for 6-12 months after the study has ended. Your identifiable details will be coded. Data will be stored in the Trust under lock and key. The computers will be password protected as per Trust policies. The Trust Confidentiality Policies, GCP guidelines, Data Protection Act 2018 and General Data Protection Regulations (GDPR) will be strictly followed at all times to ensure the confidentiality of your personal data.

Only the Chief Investigator, Principal Investigator and research team will have access to your personal data during the study. The research team is part of clinical care team.

**What will happen to the results of the research study?**

After the end of this study the results will be analysed and published in medical scientific journals. All the information you provide will be combined with the results from everyone else and it will not be possible to identify any individual from the results. It will take time for all the patients to finish this clinical study, so publication of the overall results will probably not be possible for some time. If you are interested in reading the publication of the results, please feel free to ask the research team for any information. Results will also be updated on the hospitals research and development website, which is located at:

http://www.ashfordstpeters.nhs.uk/about-us/research-and-development

**DIASMOKE Study- IRAS Project ID: 280909, PIS Version 2.1, 23 May 2020**
Who is organising and funding the study?
This study has been organised and is sponsored by ECLAT Limited, a spin off company of the University of Catania in Italy. They will reimburse St Peter’s Hospital for research team’s time including you in this study.

Who has reviewed the study?
All research in the NHS is looked at by an independent group of people, called a Research Ethics Committee, to protect your interests. This study has been reviewed and given favourable opinion by the London - Hampstead Research Ethics Committee, REC Reference number 20/LO/0704.

Contact for Further Information
Please feel free to ask any question you have about this study. If you have a concern about any aspect of this study, you should ask to speak to the researchers who will do their best to answer your questions.

Contact Details:
Name: Dr Chong Lim

Email: Chong.Lim@nhs.net
Tel No.: 0193 272 6196

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