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International Randomized 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 (word count: 292)

Reducing exposure to cigarette smoke is an imperative for public health and for diabetic patients. Increasingly, combustion-free technologies for nicotine delivery such as e-cigarettes and heated tobacco products are substituting conventional cigarettes and accelerating the current downward trends in smoking prevalence. However, there is limited information about the long-term health impact in diabetics who use these technologies.

This international, randomized, prospective, controlled trial of type 2 diabetic cigarette smokers will test the hypothesis that following a switch from conventional cigarettes to Combustion-Free Nicotine Delivery Systems (C-F NDS), a measurable improvement in metabolic syndrome (MetS) risk factors and functional parameters will be shown over the course of 2 years.

The study is multi-centre and thus will take place in five locations in five different countries in an ambulatory setting. A total of 576 diabetic patients will be randomized (1:2 ratio) to either a control arm (Study Arm A), in which they will be offered referral to smoking cessation programs or to an intervention arm (Study Arm B) assigned to C-F NDS use. Participants will be at the age of at least 23 years and of any gender. Patient recruitment will start in October 2020 and is expected to be completed by August 2021.

Primary outcome measures include fasting plasma glucose, blood pressure (BP), triglycerides, high-density lipoprotein (HDL) and waist circumference, whilst 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 timepoint.

This will be the first study determining the overall health impact of using such technologies in diabetic patients. Data from this study will provide valuable insights into the overall potential of C-F NDS to reduce the risk of cardiovascular disease in individuals, particularly diabetic patients.

Clinical Trial Registration: https://clinicaltrials.gov/ct2/show/NCT04231838

STRENGTHS AND LIMITATIONS OF THIS STUDY

Strengths

1. DIASMOKE will be the first study to determine an overall health impact of CF-NDS on diabetic patients.
2. Insights into a potential role of CF-NDS in reducing a cardiovascular risk will be given.
3. A compliance to a study protocol will be monitored daily via a mobile application.

Limitations

1. Compliance to a study protocol is crucial.
2. A study duration is limited to 24 months.

ECLAT Srl., a research spin off company of the University of Catania will be funding this study
Sponsor contact information: ECLAT Srl., Via S. Sofia 89, 95123 Catania (Italy)
A grant number is COE1-05.
Sponsor may terminate part of or the entire study for safety or administrative reasons.

Trial Management Committees

Trial Steering Committee:
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 Maurizio Di Mauro, Principal Investigator (Site 2), Italy
Prof Lorina Vudu, Principal Investigator, Moldova
Prof Farrukh Iqbal, Principal Investigator, Pakistan
Dr David Crook, Research Design Service, University of Brighton, UK

Data Monitoring & Safety Committee (see page 9 of this manuscript)

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,[1] the latter cardiovascular complications being most common, and a frequent cause of death. Besides diabetes and hyperglycemia, obesity, hypertension, dyslipidemia 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 MetS but substantially increases the risk of micro- and macrovascular complications in patients with type 2 DM (T2DM),[2-5] whereas quitting smoking substantially reduces this risk.[4-7] Given that exposure to cigarette smoke is associated with vascular damage, endothelial dysfunction and activation of coagulation and fibrinolysis,[8] it is not surprising that smoking enhances the combined harmful effects of elevated blood glucose and other risk factors and accelerates vascular damage in diabetic patients. If reducing exposure to cigarette smoke is an imperative for public health, it is even more so for patients with T2DM.[9] However, prevalence of smoking among people with DM appears to be similar to that of the general population.[10] In the United States, the prevalence of tobacco consumption has decreased substantially, but this beneficial trend has not been observed in patients with DM.[11]

There is a clear urgent need to target T2DM patients to successful smoking cessation therapies, such as nicotine-containing preparations.[12, 13] Unfortunately, there is no convincing demonstration of effective cessation interventions in patients with diabetes[14] and, in general, most smokers are reluctant to seek formal treatment for stopping smoking with the vast majority making attempts to quit without assistance.[15, 16] 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[17] and are thought to be less harmful alternative to tobacco smoking.[18-20] However, there are no long-term studies assessing cardiovascular risk or effect on cardiovascular risk factors in diabetics who use these technologies.

The DIASMOKE collaborators seek to determine whether T2DM cigarette smokers who switch to combustion-free nicotine delivery systems 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 randomized controlled study designed to determine whether T2DM cigarette smokers switching to C-F NDS experience measurable improvement in cardiovascular risk parameters as a consequence of avoiding exposure to cigarette smoke toxicants.

Study Population

The inclusion and exclusion criteria are summarized in Table 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 Table 1). Smoking status will be verified by an exhaled CO measurement (exhaled CO ≥7 ppm) at the Screening Visit. Each participant will be offered access to local free smoking cessation programs, and only those who refuse participation in cessation programs and are willing to switch to a C-F NDS will be

randomized 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.

Table 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 five consecutive years prior to the Screening Visit
Type 2 Diabetes Mellitus (as defined by the American Diabetes Association)
6.5 %<HbA1C<10 %
Body Mass Index (BMI) between 17.6 and 32.0 kg/m2 inclusive
Body weight exceeding 50 kg (males) or 40 kg (females)

Exclusion criteria

History of recent acute decompensation of their disease requiring treatment within 4 weeks prior to Visit 1.
Known clinically-significant neurological, gastrointestinal, renal, hepatic, cardiovascular, psychiatric, respiratory, metabolic, endocrine, haematological or other major 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 (e.g., 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 randomization) 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 (e.g., employee or student of the investigational site)

Study Design

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

Participants will attend a Screening Visit within 28 days prior to Visit 1 [Table 2a] and undergo demographic assessments including socio-demographic data, detailed medical history (including medication use), detailed smoking, vaping, and heated tobacco products 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 program as per local guidelines. Participants will be offered a further second opportunity to enroll in the free local smoking cessation program prior to enrollment.

Table 2a. A schedule of the study visits

Visit 0 (screening visit)	Within 28 days prior to Visit 1
Visit 1	Day 1
Visit 2	Day 90 (+/- 5 days)
Visit 3	Day 180 (+/- 7 days)
Visit 4	Day 360 (+/- 7 days)
Visit 5	Day 720 (+/- 7 days)

Following baseline assessments on Day 1 [Table 2b], participants will be randomized to either control (A) or the intervention (B) arm. The randomization 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 allocation will be provided by the software immediately after the staff randomizing the participant will access the web-based application entering their participant identification number, date of birth and initials into the program. Patients randomized into arm B will be allowed to choose the product of their preference from the given pool of most popular C-F NDS. The participants will be trained and counselled on the chosen device and given a full one week supply of tobacco sticks/e-cigarette cartridges/e-liquids refill bottles prior to check-out on Day 1. After randomization, a dedicated tracker application will be installed on patients' smartphones. The APP is designed to track patients behavior (physical activity, adherence to sugar testing, cigarette smoking frequency, daily 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, etc) throughout the whole duration of the study.

Table 2b. Assessments performed prior to randomization (Visit 1) and at each following visit (Visit 2 to Visit 5)

Review of inclusion/exclusion criteria*
Completion of Case Report Form (CRF)*
Review of concomitant medication
Number of cigarettes consumed on a daily basis
Pregnancy test (for female participants) or review of pregnancy status
Vital signs (BP, HR)
Waist circumference, height and weight, body composition (fat and skeletal muscle)
Fasting blood sample for:
Complete blood count including white cell count, Haemoglobin, platelets
Lipid profile (TG, HDL, LDL cholesterol)
Fasting glucose level, HbA1C
Insulin level for HOMA index
Plasma creatinine levels
Testosterone levels (men only)
Urine Albumin to Creatinine Ratio (ACR)
Spirometry
Carbon monoxide breath test
Fagerstrom questionnaire for Nicotine/Cigarette Dependence (FTCD)
Diabetes QoL questionnaire

*performed prior to randomization (Visit 1) only

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 2a,2b]. Following each visit participants will be supplied with an appropriate amount of consumables (tobacco sticks, e-cigarette cartridges, e-liquid refill bottles). Participants will fast overnight (from midnight) prior to each study visit at which clinical laboratory evaluations 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 randomized 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 CF-NDS and to verify product adherence, patients randomized 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 offered referral to local free cessation programs. Premature withdrawal from the study may occur if participants: 1) experiences a severe adverse event (SAE); 2) sustain any protocol deviations occur during the conduct of the study, which cannot be corrected; 3) is uncooperative, including non-attendance; 4) decide to stop his/her participation at any moment of the study; 5) becomes pregnant.
DIASMOKE is an unblinded study due to its specification.
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 GCP (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.

Patient and Public Involvement

A Focus Group of Smokers with Diabetes was organised on February 25th, 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 & Development Committee, which includes a Patient Representative.

Objectives and Endpoints

The primary objective of DIASMOKE is to assess the impact of sustained use of CF-NDS on the proportion of patients with Metabolic Syndrome, as defined by National Cholesterol Education Program (NCEP) MetS score[21] below the diagnostic threshold (<3).The primary outcome of the study will be change in prevalence of an NCEP MetS score <3 between baseline and 2 years follow-up, with comparison being made between T2DM patients randomized to each arm of the study.

Change in prevalence will also be assessed at 3 months, 6 months, and 1 year, as secondary outcomes. All assessments at each time-point will be undertaken in all participants in both arms. Considering the results of a number of lifestyle modification interventions, the absolute reduction in MetS prevalence following substantial smoking cessation is expected to be no less than 15%.[22-26]

The main prespecified secondary endpoint is an absolute change in the sum of the individual factors of the Metabolic Syndrome (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 Metabolic Syndrome (as defined by NCEP criteria) measured at each study time-point (between and within study groups) and change of the following variables 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[22-26]
- The baseline prevalence of MetS in T2DM is expected to be 70%.[27-30]

Sample size was calculated on the basis of demonstration of superiority, using an assumption of normal distribution, as described by Pocock.[31] Significance level was set at 5% ($\alpha = 0.05$), with a power of 80% ($\beta = 0.20$). 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 randomized to CF-NDS who are expected to achieve sustained reduction in cigarette consumption of at least 80% for the duration of the study ($\%_{SusRed}$).[32-36]

The adjusted number of patients in the intervention arm (N_2) was therefore increased to 320:
$N_2 = N/\%_{SusRed} = 320$ (N_2 indicating the final number of patients required after taking into consideration the 50% sustained reduction figure).
Additionally, the expected number of patients in both arms withdrawing from the trial over 2 years is estimated at 20%.[37-39] The total number of patients recruited to each treatment arm was therefore increased by this amount:
Intervention arm: 320 x 1.2 = 384
Control arm: 160 x 1.2 = 192
Total patients both arms = 576

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 randomized to the intervention arm who achieve a sustained reduction in cigarette consumption of at least 80% across the full duration of follow-up combined with all patients randomized 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 2-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 randomized 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 the efficacy and safety results of the primary analysis after six months (or otherwise if determined by the committee) and make a recommendation regarding early termination based on observed results of the study on grounds of an unfavorable 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.

A Trial Monitoring Plan will be developed and agreed by the Trial Steering Committee and Chief Investigator based on the trial risk assessment which may include on site monitoring. The Contact Research Organization (Metanoic Health Ltd) will arrange an independent Monitor. The processes reviewed can relate to participant enrolment, consent, eligibility, and allocation to trial groups; adherence to trial interventions and policies to protect participants, including reporting of harm and completeness, accuracy, and timeliness of data collection. Monitoring will be done by exploring the trial dataset or performing site visits.

Ethics and dissemination

The study will be conducted according to the Principles of Good Clinical Practice (GCP) and Declaration of Helsinki. All six local Ethics Committees reviewed and approved the study and - where appropriate - translated relevant documentation (informed consent form, patients information sheet, etc). If 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 REC (Research Ethics Committee) for approval before implementation. Any amendments will apply to all sites. At each site the Principal Investigator (PI) will retain overall responsibility for the conduct of research at their site; this includes the taking of informed consent of participants at their site. 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, in addition any equivalent local data protection regulations will be complied with. All Committee members are independent and have no conflict of interest. The Trial Steering Committee (TSC) will have access to the full trial dataset. A formal request from site investigator(s) describing their plans will require TSC and Sponsor approval.
The sponsor institution has open data access policy and the anonymized data will be available upon request to any researcher following approval from the established scientific committee. The intention 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 ASPH website where patients and members of the public will be able to access it. The trial is registered with ClinicalTrails.gov Identifier: NCT04231838.

RESULTS

Patient recruitment will start in October 2020 and enrolment is expected to be completed by August 2021. Results will be reported between 2023 and in 2024.

DISCUSSION

Little is known about the impact of combustion-free nicotine delivery systems (C-F NDS) on T2DM patients who smoke. Products that do not require combustion to deliver nicotine, such as e-cigarettes (ECs) and heated tobacco products (HTPs) are substituting conventional cigarettes globally.[17] They potentially offer substantial reduction in exposure to harmful and potentially harmful chemical constituents compared to conventional cigarettes.[18-20, 40-42] DIASMOKE will be the first study determining the overall health impact of using such technologies in diabetic patients. Undoubtedly, it is desirable for patients to avoid consumption of any tobacco related inhalation products, but in order for Governments and clinicians to provide guidance about cigarette substitution, robust evidence-based information is required.

We designed this international RCT (Randomized Controlled Trial) 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 T2DM patients who smoke switch to using C-F NDS compared with T2DM patients who continue to smoke conventional cigarettes. Several parameters measured in this study are associated with the development 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.[43-44] Consequently, the profile of these changes after switching to CF-NDS could provide valuable insights into the overall potential of CF-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, hence 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 diabetic patients. Clearly, randomization will equalize 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 cessation smoking programs.

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 randomized 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 APP. Although not expected that compliance for this study will be materially different compared to other comparable studies, our power calculations are over-estimated to take account of a non-compliance rate of 50%. Thus, the C-F NDS population will be oversampled by adopting a 1:2 randomization ratio scheme (i.e. for every patient randomized in the control population, two will be randomized 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 re-supply of tobacco sticks/e-cigarette cartridges/e-liquids refill bottles.

This study has several innovative features. To improve adherence to C-F NDS (and maximize overall compliance to the study protocol), patients randomized to switching to C-F NDS use 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 can ensure a likely user-friendly experience (i.e. 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 generalizability.

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 diabetic patients.

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Figure 1. Study design of DIASMOKE. Flow chart summarizing the study design. Initial Screening Visit will be followed by Visit 1, during which participants will be randomized to one of the study arms (Arm A and B). Patients in both arms will be invited to attend further clinical visits (V2-V5). All participants will be given an opportunity to enroll in the free local smoking cessation program at each visit.

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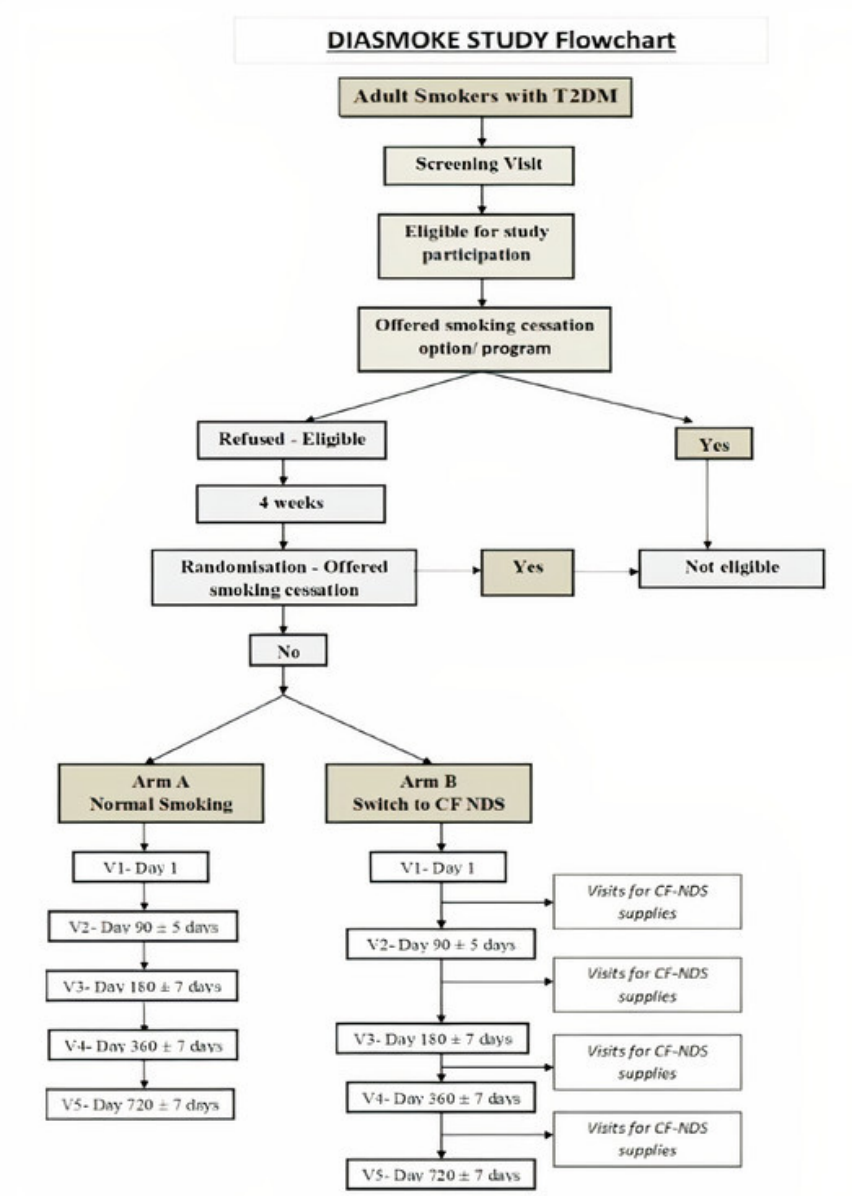

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44x62mm (300 x 300 DPI)

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		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	1
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	2
Protocol version	#3	Date and version identifier	1
Funding	#4	Sources and types of financial, material, and other support	2
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1

Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	2
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	2
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	3
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	4
Objectives	#7	Specific objectives or hypotheses	4
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	5
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will	4

		perform the interventions (eg, surgeons, psychotherapists)	
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	6
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	7
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	6
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	7
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	8
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	5
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	7
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	4
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	6

Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	6
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	6
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	7
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n/a
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	6
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	6
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	7
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	9
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	8

Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	8
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	9
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	9
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	9
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	9
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	9
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	9
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	9
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	9
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	5

Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	9
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	9
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	9
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	9
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	9
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	9
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	9
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a

BMJ Open

International Randomized 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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International Randomized 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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Introduction

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

Methods and Analysis

The study is multicenter and thus will take place in five locations in four countries in an ambulatory setting. A total of 576 diabetic patients will be randomized (1:2 ratio) to either a control arm (Study Arm A), in which they will be offered referral to smoking cessation programs 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 (BP), triglycerides, high-density lipoprotein (HDL) and waist circumference, whilst 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 timepoint.

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 favorable opinion. The results of the study are intended to be published as articles in high quality peer-reviewed journals and disseminated through conference papers.

Clinical Trial Registration: https://clinicaltrials.gov/ct2/show/NCT04231838

STRENGTHS AND LIMITATIONS OF THIS STUDY

Strengths

1. DIASMOKE will be the first study to determine an overall health impact of C-F NDS in diabetes and its cardiovascular risk.
2. Adherence to C-F NDS will be strengthened by providing a wide variety of different products to meet patients' preference.
3. Compliance to the study protocol will be monitored daily via a mobile application.

Limitations

1. Due to the relatively long duration of the study, adequate participants' retention may be challenging.
2. Study results cannot be generalized to people with T1DM or with unstable T2DM.

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Dr Jonathan Belsey of JB Medical is commissioned by the Funder for data analysis and interpretation.

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The contents, selection and presentation of facts, as well as any opinions expressed in the paper are the sole responsibility of the authors and under no circumstances shall be regarded as reflecting the positions of the Foundation for a Smoke-Free World. The Grantor had no role in the selection of the research topic, study design, or the writing of the paper or the project.

Trial Management Committees

Trial Steering Committee:

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.

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Dr Chong Lim, Principal Investigator, UK
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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,[1] the latter cardiovascular complications being most common, and a frequent cause of death. Besides diabetes and hyperglycemia, obesity, hypertension, dyslipidemia 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 MetS but substantially increases the risk of micro- and macrovascular complications in patients with type 2 DM (T2DM),[2-5] whereas quitting smoking substantially reduces this risk.[4-7] Given that exposure to cigarette smoke is associated with vascular damage, endothelial dysfunction and activation of coagulation and fibrinolysis,[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 diabetic patients.

If reducing exposure to cigarette smoke is an imperative for public health, it is even more so for patients with T2DM.[11] However, prevalence of smoking among people with DM appears to be similar to that of the general population.[12] In the United States, the

prevalence of tobacco consumption has decreased substantially, but this beneficial trend has not been observed in patients with DM.[13]

There is a clear urgent need to target T2DM patients to successful smoking cessation therapies, such as nicotine-containing preparations.[14, 15] Unfortunately, there is no convincing demonstration of effective cessation interventions in patients with diabetes[16] and, in general, most smokers are reluctant to seek formal treatment for stopping smoking with the vast majority making attempts to quit without assistance.[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[19] and are thought to be less harmful alternative to tobacco smoking.[20-22] However, there are no long-term studies assessing cardiovascular risk or effect on cardiovascular risk factors in diabetics who use these technologies.

The DIASMOKE collaborators seek to determine whether T2DM cigarette smokers who switch to combustion-free nicotine delivery systems 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, multicenter, open label randomized controlled study analyzing two parallel groups of participants, designed to determine whether T2DM cigarette smokers switching to C-F NDS experience measurable improvement in cardiovascular risk parameters as a consequence of avoiding exposure to cigarette smoke toxicants.

Study Population

The inclusion and exclusion criteria are summarized in Table 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 Table 1). Smoking status will be verified by an exhaled CO measurement (exhaled CO ≥7 ppm) at the Screening Visit. Each participant will be offered access to local free smoking cessation programs, and only those who refuse participation in cessation programs and are willing to switch to a C-F NDS will be randomized 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.

Table 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 five consecutive years prior to the Screening Visit
Type 2 Diabetes Mellitus (as defined by the American Diabetes Association)
6.5 %<HbA1C<10 %
Body Mass Index (BMI) between 18.5 and 34.9 kg/m2 inclusive
Body weight excess of at least 50 kg (males) or 40 kg (females)
Exhaled Carbon Monoxide (CO) 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 1.
Known clinically-significant neurological, gastrointestinal, renal, hepatic, cardiovascular, psychiatric, respiratory, metabolic, endocrine, haematological or other major 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 (e.g., 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 randomization) 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 (e.g., employee or student of the investigational site)

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 2a] and undergo demographic assessments including socio-demographic data, detailed medical history (including medication use), detailed smoking, vaping, and heated tobacco products 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 program as per local guidelines. Participants will be offered a further second opportunity to enroll in the free local smoking cessation program prior to enrollment.

Table 2a. A schedule of the study visits

Visit 0 (screening visit)	Within 28 days prior to Visit 1
Visit 1	Day 1
Visit 2	Day 90 (+/- 5 days)
Visit 3	Day 180 (+/- 7 days)
Visit 4	Day 360 (+/- 7 days)
Visit 5	Day 720 (+/- 7 days)

Following baseline assessments on Day 1 [Table 2b], participants will be randomized to either control (A) or the intervention (B) arm. The randomization 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 allocation will be provided by the software immediately after the staff randomizing the participant will access the web-based application entering their participant identification number, a month and a year of birth and initials into the program. Patients randomized into arm B will be allowed to choose the product of their preference from the given pool of most popular C-F NDS. The participants will be trained and counselled on the chosen device and given a full one week supply of tobacco sticks/e-cigarette cartridges/e-liquids refill bottles prior to check-out on Day 1. After randomization, a dedicated tracker application will be installed on patients' smartphones. The APP is designed to track patients behavior (physical activity, adherence to sugar testing, cigarette smoking frequency, daily 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, etc.) throughout the whole duration of the study.

Table 2b. Assessments performed prior to randomization (Visit 1) and at each following visit (Visit 2 to Visit 5)

Review of inclusion/exclusion criteria*
Completion of Case Report Form (CRF)*
Review of concomitant medication
Number of cigarettes consumed on a daily basis
Pregnancy test (for female participants) or review of pregnancy status
Vital signs (BP, HR)
Waist circumference, height and weight, body composition (fat and skeletal muscle)
Fasting blood sample for:
Complete blood count including white cell count, Haemoglobin, platelets
Lipid profile (TG, HDL, LDL cholesterol)
Fasting glucose level, HbA1C
Insulin level for HOMA index
Plasma creatinine levels
Testosterone levels (men only)
Urine Albumin to Creatinine Ratio (ACR)
Spirometry
Carbon monoxide breath test
Fagerström questionnaire for Nicotine/Cigarette Dependence (FTCD)
Diabetes QoL questionnaire

*performed prior to randomization (Visit 1) only

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 2a,2b]. Following each visit participants will be supplied with an appropriate amount of consumables (tobacco sticks, e-cigarette cartridges, e-liquid refill bottles). Participants will fast overnight (from midnight) prior to each study visit at which clinical laboratory evaluations 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 randomized 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 randomized 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 offered referral to local free cessation programs.

Premature withdrawal from the study may occur if participants: 1) experiences a severe adverse event (SAE); 2) sustain any protocol deviations occur during the conduct of the study, which cannot be corrected; 3) is uncooperative, including non-attendance; 4) decide to stop his/her participation at any moment of the study; 5) becomes pregnant.

DIASMOKE is an unblinded study due to its specification.
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 GCP (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 individual patient will be allocated a Case Report Form (CRF). CRF will be an electronic document. The CRF data will be used to perform statistical analysis for the trial. Anonymized 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 QoL (Quality of Life) Questionnaire or Fagerstrom Test For Nicotine Dependence (FTND). 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 February 25th, 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 & 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[23] below the diagnostic threshold (<3).The primary outcome of the study will be change in prevalence of an NCEP MetS score <3 between baseline and 2 years follow-up, with comparison being made between T2DM patients randomized to each arm of the study.

Change in prevalence will also be assessed at 3 months, 6 months, and 1 year, as secondary outcomes. All assessments at each time-point will be undertaken in all participants in both arms. Considering the results of a number of lifestyle modification interventions, the absolute reduction in MetS prevalence following substantial smoking cessation is expected to be no less than 15%.[24-28]

The main prespecified secondary endpoint is an absolute change in the sum of the individual factors of the Metabolic Syndrome (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 Metabolic Syndrome (as defined by NCEP criteria) measured at each study time-point (between and within study groups) and change of the variables given in Table 2b 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]

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% ($\alpha = 0.05$), with a power of 80% ($\beta = 0.20$). 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 randomized 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 (N_2) was therefore increased to 320:
$N_2 = N/\%_{SusRed} = 320$ (N_2 indicating the final number of patients required after taking into consideration the 50% sustained reduction figure).
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 x 1.2 = 384
Control arm: 160 x 1.2 = 192
Total patients both arms = 576
In order to reach the target sample size diabetic patients 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 app.

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 randomized to the intervention arm who achieve a sustained reduction in cigarette consumption of at least 80% across the full duration of follow-up combined with all patients randomized 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 2-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 randomized 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 the efficacy and safety results of the primary analysis after six months (or otherwise if determined by the committee) and make a recommendation regarding early termination based on observed results of the study on grounds of an unfavorable 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 and Chief Investigator based on the trial risk assessment which may include on site monitoring. The Contact Research Organization (Metanoic Health Ltd) will arrange a monitor independent from investigators and the sponsor. The processes reviewed can relate to participant enrolment, consent, eligibility, and allocation to trial groups; adherence to trial interventions and policies to protect participants, including reporting of harm and completeness, accuracy, and timeliness of data collection. Monitoring will be done by exploring the trial dataset or performing site visits.

Adverse and serious adverse events (AE and SAE) will be noted during the whole duration of the study. AEs and SAEs will be recorded at 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 (GCP) and Declaration of Helsinki. All five local Ethics Committees reviewed and approved the study and - where appropriate - translated relevant documentation (informed consent form, patients information sheet, etc.). A list of the ethics committees that reviewed and approved the study is attached as supplementary information file.[Supplementary File 1] If 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 REC (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 below).

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 local data protection regulations will be complied with.

The Trial Steering Committee (TSC) will have access to the full trial dataset. 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 (ASPH) website where patients and members of the public will be able to access it. The sponsor institution has open data access policy and the anonymized data will be available upon request to any researcher following approval from the established scientific committee.

The informed consent materials (Consent Form and Patient Information Sheet) are attached as supplementary information files. [Supplementary File 2, Supplementary File 3]

The trial is registered with ClinicalTrials.gov Identifier: NCT04231838.

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 in 2024.

DISCUSSION

Little is known about the impact of combustion-free nicotine delivery systems (C-F NDS) on T2DM patients who smoke. Products that do not require combustion to deliver nicotine, such as e-cigarettes (ECs) and heated tobacco products (HTPs) are substituting conventional cigarettes globally.[19] They potentially offer substantial reduction in exposure to harmful and potentially harmful chemical constituents compared to conventional cigarettes.[20-22, 42-44] DIASMOKE will be the first study determining the overall health impact of using such technologies in diabetic patients. Undoubtedly, it is desirable for patients to avoid consumption of any tobacco related inhalation products, but in order for Governments, health authorities (e.g. EMEA, FDA) and clinicians to provide guidance about cigarette substitution, robust evidence-based information is required.

We designed this international RCT (Randomized Controlled Trial) 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 T2DM patients who smoke switch to using C-F NDS compared with T2DM patients who continue to smoke conventional cigarettes. Several parameters measured in this study are associated with the development 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.[45-46] Consequently, 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, hence 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 diabetic patients. Clearly, randomization will equalize 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 cessation smoking programs.

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 randomized 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 APP. Although not expected that compliance for this study will be materially different compared to other comparable studies, our power calculations are over-estimated to take account of a non-compliance rate of 50%. Thus, the C-F NDS population will be oversampled by adopting a 1:2 randomization ratio scheme (i.e. for every patient randomized in the control population, two will be randomized 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 re-supply of tobacco sticks/e-cigarette cartridges/e-liquids refill bottles.

This study has several innovative features. To improve adherence to C-F NDS (and maximize overall compliance to the study protocol), patients randomized to switching to C-F NDS use 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 can ensure a likely user-friendly experience (i.e. 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 generalizability.

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 generalized to all diabetic patients 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 is some countries. A competitive recruitment strategy and staggered activation of clinical sites less impacted by the pandemic, will be implemented to minimize 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 diabetic patients.

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Figure 1. Study design of DIASMOKE. Flow chart summarizing the study design. Initial Screening Visit will be followed by Visit 1, during which participants will be randomized to one of the study arms (Arm A and B). Patients in both arms will be invited to attend further clinical visits (V2-V5). All participants will be given an opportunity to enroll in the free local smoking cessation program at each visit.

AUTHOR STATEMENT

Arkadiusz Krysinski - manuscript drafting and revision.
Cristina Russo - study design, literature review, manuscript drafting and revision.
Sarah John - manuscript drafting and revision.
Jonathan Belsey - sample size and statistical analysis plan
Davide Campagna - study design, literature review, manuscript drafting and revision.
Pasquale Caponnetto - study design, manuscript drafting and revision.
Lorina Vudu - manuscript revision.
Chong Wei Lim - manuscript revision.
Francesco Purrello - manuscript revision.
Maurizio Di Mauro - manuscript revision.
Farrukh Iqbal - manuscript revision.
David Fluck - manuscript revision.
Edward Franek - manuscript drafting and revision.
Riccardo Polosa - manuscript drafting and revision.
Pankaj Sharma - study design, manuscript drafting and revision.

The services of professional writers were not used.

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COMPETING INTERESTS STATEMENT

All Trial Steering Committee members are independent and have no conflict of interest.

Metanoic Health Limited will be responsible for the overall Trial Management and Monitoring. There is no conflict of interest with Sponsor.

However, Dr Isaac John, CEO of Metanoic Health Ltd is employed as Deputy Director of R&D at Ashford and St Peter's Hospitals NHS Foundation Trust.

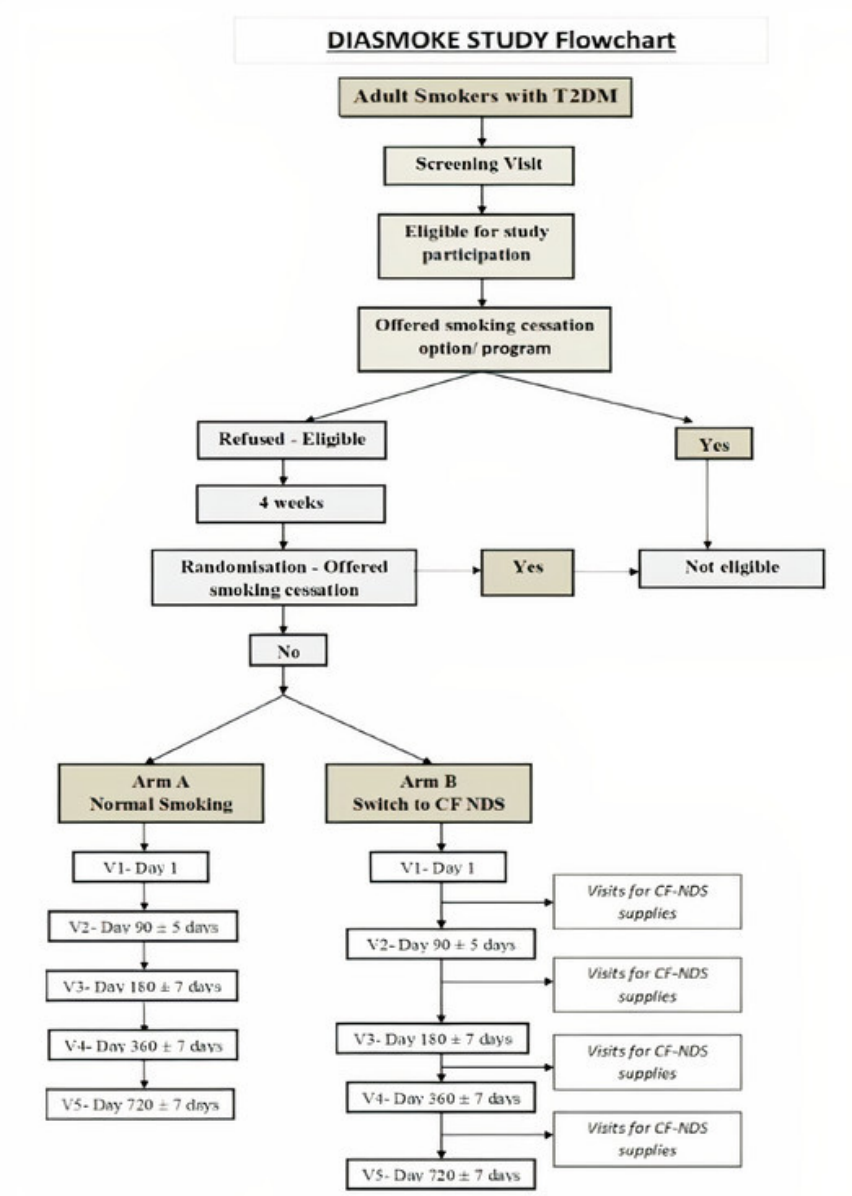

Figure 1. Study design of DIASMOKE. Flow chart summarizing the study design. Initial Screening Visit will be followed by Visit 1, during which participants will be randomized to one of the study arms (Arm A and B). Patients in both arms will be invited to attend further clinical visits (V2-V5). All participants will be given an opportunity to enroll in the free local smoking cessation program at each visit.

44x62mm (300 x 300 DPI)

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: _____

		Please initial each box
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

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

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/
- 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 persona 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

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

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. BMJ. 2013;346:e7586

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	1-2
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	Yes (available in trial register NCT04231838)
Protocol version	#3	Date and version identifier	1
Funding	#4	Sources and types of financial, material, and other support	3
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1, 19

Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	3
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	3
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	4
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4-5
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	12-13
Objectives	#7	Specific objectives or hypotheses	5, 9
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	5, 7
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be	6

		obtained	
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	5-6
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	6-8
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	8
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	7-8, 13
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	8
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	9
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	6-8
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	9-10
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	10

Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	7
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	7
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	7-8
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	8
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n/a
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the	8

		protocol	
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	8, 13-14
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	8
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	10
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	10
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	10
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	10-11
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	11
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	11

Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	11
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	11
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	11
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	11 (see appendices)
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	11 (see appendices)
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	11-12
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	19
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	12
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	12; See appendix (Patient Information Sheet)
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing	12

		arrangements), including any publication restrictions	
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	19
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	12
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	12 (see appendices)
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a

Notes:

- 2b: Yes (available in trial register NCT04231838)
- 26a: 11 (see appendices)
- 26b: 11 (see appendices)
- 30: 12; See appendix (Patient Information Sheet)
- 32: 12 (see appendices) The SPIRIT checklist is distributed under the terms of the Creative Commons Attribution License CC-BY-ND 3.0. This checklist was completed on 24. January 2021 using https://www.goodreports.org/, a tool made by the EQUATOR Network in collaboration with Penelope.ai