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Exenatide as an adjunct to nicotine patch for smoking cessation and prevention of postcessation weight gain among treatment-seeking smokers with pre-diabetes and/or overweight: study protocol for a randomised, placebo-controlled clinical trial

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STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This trial will examine the glucagon-like peptide 1 receptor as a novel target for smoking cessation and postcessation weight management.
⇒ This trial will use a randomised, double-blinded, placebo-controlled design with prespecified outcome measures and intention-to-treat analysis.
⇒ Building on our previous 6-week trial of exenatide, the current study will extend the treatment duration to 14 weeks and include a follow-up at 12 weeks post end of treatment.
⇒ By assessing neuroaffective responses to nicotine-related and food-related stimuli via electroencephalogram, the trial will provide a potential mechanism for the efficacy of exenatide in this population of smokers.
⇒ A potential limitation of the trial is the focus on smokers who are prediabetic and/or overweight, which may limit the generalisability of the findings.

INTRODUCTION

Obesity remains a major public health crisis with widespread impact on healthcare costs, quality of life and mortality. US prevalence data indicate that the majority (i.e. 74%) of American adults are overweight/obese - a
10% increase from 2000. The only risk factor currently surpassing obesity as the leading cause of preventable morbidity and mortality is cigarette smoking. Approximately 400,000 Americans die each year from smoking-related causes, and 16 million Americans live today with a smoking-related disease.

Although the health benefits of achieving smoking abstinence are extensive, including reductions in cardiovascular disease, chronic obstructive pulmonary disease and cancer risks, approximately 80%-90% of those who quit smoking experience rapid and significant weight gain, which partially attenuates these benefits. On average, former smokers gain 5–15 pounds of body weight within the first few months of quitting, and a non-trivial proportion of quitters gain more than 20 pounds. Postcession weight gain (PCWG) is problematic for several reasons. First, concerns about PCWG prevent some people from initiating a quit attempt. Second, PCWG can be a cause of relapse. Third, PCWG can worsen metabolic health, leading to the development or progression of obesity and type 2 diabetes (T2D), potentially contributing to premature morbidity and mortality associated with these diseases.

Glucagon like peptide-1 (GLP-1) is produced in intestinal L-cells and released from the gut in response to food intake. By stimulating insulin secretion and inhibiting glucagon secretion, GLP-1 regulates postprandial glucose excursions. GLP-1 is also known to stimulate centrally mediated appetite control and satiety. Notably, GLP-1 receptor agonists (GLP-1RA) are currently used for the treatment of T2D and weight management in people with and without T2D. GLP-1 receptors are expressed in many brain regions. In addition to the hypothalamus and brain stem, GLP-1 receptors are expressed throughout the mesolimbic dopamine system, and GLP-1 containing neurons extend directly into the ventral tegmental area and nucleus accumbens. These brain regions are intimately associated with the regulation of food-related and nicotine-related reward. Consistent with this, preclinical studies have shown that GLP-1RAs significantly decrease nicotine self-administration and attenuate nicotine conditioned place preference.

Further, our recent clinical trial of a GLP-RA extended-release exenatide showed that in the sample of 82 smokers who were prediabetic and/or overweight, 6 weeks treatment with exenatide resulted in a higher probability of abstinence and a lower probability of PCWG, compared with placebo. The objective of the current phase II clinical trial is to extend these promising findings by: (1) investigating the robustness of exenatide’s effects following a longer treatment and post-treatment period and (2) exploring putative mechanisms through which exenatide might facilitate smoking cessation and mitigate PCWG. Recent calls have been made for an experimental therapeutic approach to designing clinical trials in which the focus is not on testing whether an intervention works but on gaining insight into how an intervention works through hypothesised target mechanisms.

METHODS AND ANALYSIS

Study design

This clinical trial will use a randomised, double-blind, placebo-controlled design and will be conducted at two US sites, the University of Texas Health Science Center at Houston (UTHHealth), Center for Neurobehavioral Research on Addiction (CNRA) and Michael E. DeBakey VA Medical Center (MEDVAMC). The sample will consist of 216 treatment-seeking adult smokers who have pre-diabetes and/or are overweight. Participants will be randomised (1:1) to receive exenatide, 2 mg or placebo (sterile saline, 0.9%), subcutaneously, once weekly for 14 weeks. All participants will receive nicotine replacement therapy (NRT, nicotine patches) for daily use and individual smoking cessation counselling. Participants will attend weekly clinic visits to receive exenatide/ placebo and NRT and complete assessments of smoking frequency and quantity, breath carbon monoxide (CO) levels, weight and other assessments. Electroencephalogram (EEG) will be conducted at baseline and before the quit attempt to assess neuroaffective responses to food, nicotine and emotional stimuli. Primary outcomes (end-of-treatment abstinence and weight change) will be assessed at 12 weeks post-target quit day. Participants will return for a follow-up visit 12 weeks after the end of treatment (24 weeks post-target quit day) for the assessment of weight and smoking status.

Study aims

Specific aims

Aim 1: To determine if exenatide improves end-of-treatment smoking abstinence rates.

Hypothesis 1: Compared with placebo, treatment with exenatide will result in a higher rate of 4-week continuous abstinence (self-reported and biochemically verified by expired breath CO levels) at 12 weeks post-target quit day.

Aim 2: To determine if exenatide mitigates PCWG.

Hypothesis 2: Compared with placebo, treatment with exenatide will be associated with reduced PCWG at 12 weeks post-target quit day.

Exploratory aims

Aim 3: To assess the effect of exenatide on post-treatment abstinence and weight.

Hypothesis 3a: Compared with placebo, treatment with exenatide will result in a higher rate of 4-week continuous abstinence (self-reported and biochemically verified) at 24 weeks post-target quit day.

Hypothesis 3b: Compared with placebo, treatment with exenatide will be associated with lower PCWG at 24 weeks post-target quit day.

Aim 4: To explore the effect of exenatide on neuroaffective responses to food-related, nicotine-related and emotional stimuli.

Hypothesis 4: Treatment with exenatide will be associated with an attenuation of event-related potential (ERP) reactivity specific to nicotine-related and food-related stimuli at week 3, relative to baseline ERP reactivity.
Participants

Eligibility
Participants will be 216 males and females between ages 18 and 75 years who report smoking 5 or more cigarettes per day for at least the past year and state a desire to quit smoking (defined as ‘intend to quit within 1 month’). Participants must have glycylated haemoglobin (HbA1C) levels between 5.7% and 6.4% and/or a body mass index (BMI) of ≥25 kg/m².

The following exclusion criteria will be applied: (1) personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2; (2) history of pancreatitis or risk of pancreatitis; (3) T1D or T2D mellitus; (4) severe cardiovascular disease (history of myocardial infarction, life-threatening arrhythmia or worsening angina pectoris); (5) severe gastrointestinal disease (ie, severe gastroparesis); (6) creatinine clearance <45 mL/min or end-stage renal disease; (7) psychotic or bipolar disorder, or mood disorder with psychotic features, or eating disorder (existing diagnosis or as determined by the structured interview); (8) moderate to high risk of suicidality; (9) psychoactive substance abuse or dependence (excluding nicotine dependence) within the past 3 months; (10) current use of glucose lowering medications; smoking cessation medications, medications used for weight management, or medications known to impact weight; (11) current use of chewing tobacco, snuff, snus or electronic cigarettes; (12) previous medically adverse reaction to study medications or nicotine; (13) women who are currently pregnant or lactating, or of childbearing potential and are not using medically accepted forms of contraception and (14) any illness or condition which in the opinion of the principal investigator (PI) and/or the study physician would preclude safe and/or successful completion of the study.

Discontinuation/withdrawal criteria
The participant may be discontinued at any time during the study at the discretion of the PI and/or the study physician for safety, behavioural, compliance or administrative reasons. Efforts must be made to have the participants, who discontinue the study medication, to continue in the study. Only participants who withdraw consent will be considered as withdrawn from the study.

Screening
Participants will be recruited using various strategies, including flyers, posters, newspapers and companies that provide recruitment services for clinical research using online platforms. Potential participants will complete a brief telephone prescreen to determine initial eligibility. The prescreen assessment includes questions assessing medical and psychiatric history, psychoactive substance use and smoking history. Based on the initial prescreen, individuals who appear eligible will be invited for a face-to-face screening visit.

The screening will begin with the completion of the informed consent (see online supplemental material) which will be obtained by the PI or designee. Informed consent procedures will include details of the study, potential risks, study timeline and voluntariness of participation and dropping out. Following informed consent, each participant will complete demographic, medical and smoking history assessments and undergo a psychiatric evaluation and physical examination. Blood samples will be collected to examine complete blood count (CBC), comprehensive metabolic panel (CMP), pancreatic enzymes and HbA1C levels. Urine samples will be collected to assess cotinine levels and to rule out drug use and pregnancy (in women of childbearing potential).

Study visits
After determining study eligibility, qualified participants will return to the clinic once a week for 14 treatment visits. Visits will include assessments of vital signs, adverse events (AEs) and concomitant medications; administration of exenatide/placebo and dispensation of nicotine patches for the upcoming week; smoking cessation counselling; and completion of various assessments as detailed in the Data collection and measures subsection and table 1.

Randomisation
The allocation orders, represented by a randomly assigned blinding coded letter for each treatment condition, will be generated with a pseudorandom number generator and uploaded to an electronic database (REDCap), which will be used to implement randomisation at both sites. The allocation ratio will be 1:1 (exenatide, placebo) and imbalanced randomised orders will be rejected to maintain balanced recruitment.

Participants, investigators and care givers performing assessments and persons performing data analysis will remain blinded to the participants’ assigned conditions (exenatide, placebo). An unblinded study nurse will maintain a hard copy of the blinding codes for each treatment condition in a secure, locked location. A password-protected field will also be uploaded to REDCap that contains the unblinding codes if emergency unblinding is required.

Intervention
Exenatide/placebo
Exenatide will be purchased commercially as Bydureon for subcutaneous injection and administered at a dose of 2 mg once a week for a total of 14 weeks (2 weeks before the target quit day and 12 weeks post-target quit day). Exenatide is supplied as a powder with a solvent for once-weekly injection. Each single-dose, dual-chamber pen contains 0.65 mg of diluent and 2 mg of exenatide, which remain isolated until mixed. An unblinded study nurse not involved in behavioural counselling, data collection or outcome measurement will prepare and administer medication. Patients will be blindfolded while receiving the injections.
Sterile saline (0.9%) will serve as the placebo for exenatide. The placebo will be administered in the same manner and volume as exenatide using insulin syringes.

Nicotine replacement therapy
Nicotine patches (generic) will be purchased commercially and dispensed during clinic visits for 1 week of use. Participants will be instructed to use one patch daily starting 2 weeks before their target quit day for a total of 14 weeks. Participants who smoke >10 cigarettes/day will use 21 mg patches for the first 12 weeks, 14 mg patches for week 13 and 7 mg patches for week 14. Participants who smoke 5–10 cigarettes per day will use 14 mg patches.

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<td>1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16</td>
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Baseline, eligibility and safety measures
- Consent, demographics, medical history, physical exam, psych (MINI)
- Smoking status (FTND, urine cotinine)
- Vital signs, prior and concomitant meds
- AE/SAE

Medications and adherence
- Randomisation
- Exenatide/placebo administration
- Nicotine patch dispensation
- Nicotine patch adherence

Smoking-related measures and analyses
- Breath CO
- Smoking frequency and quantity (TLFB)
- Withdrawal and craving (WSWS, QSU, mCEQ)
- 4 week continuous abstinence
- 7 day point prevalence abstinence

Weight-related and diet-related measures
- Weight
- BMI
- Waist circumference
- Food craving (FCI)
- Diet and physical activity (ASA24, GPAQ)

Other measures (self-report and mechanism)
- Psychiatric (PANAS, PHQ-8)
- Mechanism (EEG)
- Laboratory assessments
- Urine drug screen, urine cotinine, CBC, CMP, amylase, lipase
- HbA1C
- Lipid panel
- Fingerstick blood glucose
- Urine pregnancy test

AE, adverse event; ASA24, Automated Self-Administered 24 hours Dietary Assessment Tool; BMI, body mass index; CBC, complete blood count; CMP, complete metabolic panel; CO, carbon monoxide; EEG, electroencephalogram; FCI, Food Craving Inventory; FTND, Fagerstrom Test for Nicotine Dependence; F/U, follow-up; GPAQ, global physical activity questionnaire; HbA1C, glycosylated haemoglobin; mCEQ, Modified Cigarette Evaluation Questionnaire; MINI, Mini-International Neuropsychiatric Interview; NRT, nicotine replacement therapy; PANAS, Positive and Negative Affect Scale; PHQ, Patient Health Questionnaire; QSU, Questionnaire of Smoking Urges; SAE, serious AE; TLFB, time line follow back; WCS, Weight Concern Scale; WEADS, Weight Efficacy after Quitting Scale; WSWS, Wisconsin Smoking Withdrawal Questionnaire.
for the first 12 weeks and 7 mg patches for weeks 13 and 14. To estimate patch adherence, participants will be instructed to return all used and unused patches. Patch adherence will be defined as wearing the patch for ≥6 of 7 days/week across the 14 weeks.

Discontinuation of the study medication
Discontinuation of the study medication can be decided by either the PI or the participant. Participants who discontinue the study medication will be encouraged to continue with the scheduled visits and assessments to ensure continued counselling and data collection.

Smoking cessation counselling
All participants will receive brief individual behavioural smoking cessation counselling based on the US Clinical Practice Guidelines, as recommended for use with pharmacotherapy. Counselling will not include recommendations on weight management strategies to directly assess the pharmacological effect of exenatide on changes in weight. The manual-driven counselling protocol has been used in previous studies and consists of once a week in-person sessions and 2 brief (10–15 min) supportive phone calls (at prequit and again at 3 days postquit), spanning the 14-week active treatment phase. Counseling will be provided by master’s level clinicians who will be trained by a clinical psychologist (JS) with extensive experience in developing counselling protocols and evaluating behavioural treatment fidelity in clinical trials of substance use disorders. Counselling sessions will be audiotaped, with 20% of sessions randomly selected to assess adherence and competence.

Participant adherence to study procedures
Throughout the study, the study staff will remind the participants to follow the study procedures and requirements to ensure participant compliance. If a participant is found to be non-compliant, the she/he will be reminded regarding the importance of following the instructions given.

Data collection and measures
Please refer to Table 1 for time points.

Smoking-related assessments
Baseline smoking status will be assessed via self-reported smoking of ≥5 cigarettes/day for ≥1 year and confirmed by a urinary cotinine test.

Nicotine dependence will be assessed using the Fagerstrom Test for Nicotine Dependence.

Smoking frequency and quantity will be assessed using the time-line follow-back (TLFB) interview methodology.

Breath CO will be assessed using a CO monitor (MicroSmokerlyzer, Williamsburg, Virginia USA).

Withdrawal symptoms will be assessed using the Wisconsin Scale of Withdrawal Symptoms (WSWS).

Covariates for cigarettes will be evaluated using the Questionnaire of Smoking Urges (QU).

Smoking satisfaction and psychological reward from smoking in subjects who report smoking between the visits will be evaluated using the Modified Cigarette Evaluation Questionnaire (mEQ).

Weight-related and diet-related assessments
Weight (kg) will be measured without shoes using a medical grade digital scale. Height (cm) will be measured without shoes using stadiometer. Waist circumference (cm) will be measured without clothes, midway between the lower rib margin and iliac crest using measure tape.

Baseline weight concerns and weight efficacy (ie, self-efficacy for preventing PCWG) will be assessed during the screening visit using the Weight Concern Scale (WCS) and Weight Efficacy after Quitting Scale, respectively.

Diet will be assessed using the Automated Self-Administered 24-hours Dietary Assessment Tool.

Craving for food will be assessed using the Food Craving Inventory (FCI).

Physical Activity will be assessed using the WHO Global Physical Activity Questionnaire.

Psychiatric/substance use assessments
Psychiatric/substance use history will be assessed using the Mini-International Neuropsychiatric Interview.

Depressive Symptoms will be assessed using Patient Health Questionnaire-8 (PHQ-8).

Positive and negative affect will be assessed using the positive and negative affect schedule (PANAS).

Laboratory assessments
Blood tests will include analyses of CBC, CMP, pancreatic enzymes (amylase and lipase), HbA1C, lipids and fingerstick blood glucose; urine tests will include analysis of cotinine, drug screen and pregnancy test in women of childbearing potential; and breath tests will include assessments of CO levels.

Electroencephalogram
EEG will be recorded with a 64-channel actiCAP active electrode cap, amplified with BrainAmp MR and digitised with Brain Vision Recorder (CNRA) or amplified with actiCHamp and digitised with PyCorder (MEDVAMC) (Brain Products, Munich). Procedures for data collection and data reduction will be similar to those used in previous studies. For each participant, the average ERP will be computed at each scalp site for each category (ie, pleasant, unpleasant, neutral, food and cigarette related) and, in line with previously published reports and methodological recommendations, the amplitude of the late positive potential (LPP) between 400 and 800 ms over a priori selected central and parietal sites will be computed. The steps outlined above for the EEG/ERP data reduction and the statistical analyses on the EEG will be performed using software (ie, BESA, Brain Vision Analyzer, SPSS, STATA, SAS and R) tested in previous studies.
Outcome measures

Primary outcomes
1. Percentage of participants with 4-week continuous abstinence at 12 weeks post-target quit day, defined as no smoking, not even a puff, as measured by self-report (TLFB) and biochemically verified (CO ≤ 5 ppm).
2. Weight change in kilograms at 12 weeks post-target quit day.

Secondary outcomes
1. Percentage of participants with 4-week continuous abstinence at 24 weeks post-target quit day as measured by self-report (TLFB) and biochemically verified (CO ≤ 5 ppm).
2. Weight change in kilograms at 24 weeks post-target quit day.
3. Amplitude of the late positive potential evoked by visual stimuli.

Other outcomes
1. Seven-day point prevalence abstinence at 12 and at 24 weeks post-target quit day.
2. Changes in BMI, waist circumference, HbA1C and serum triglyceride levels.
3. Smoking satisfaction (mCEQ score) in participants who report smoking between visits.
4. Craving for cigarettes (QSU score).
5. Withdrawal symptoms (WSWS score).
6. Craving for highly palatable food (FCI score).
7. Depressive symptoms (PHQ-8 score) and affect (PANAS score).

Safety and monitoring

Medical monitoring
Vital signs and overall well-being will be assessed at each visit. Blood glucose levels will be assessed prior to each dose of exenatide. Subsequent doses of the study medication will not be administered if any of the following occur or suspected: acute pancreatitis, hypoglycaemia (blood glucose < 70 mg/dL), severe injection site reaction, anaphylaxis, angioedema, acute kidney injury or if the study physician believes that there may be any reason to withhold the study medication.

AE assessment and management
Careful clinic procedures will be followed to avoid any potential harm to participants from possible adverse medical or psychological reactions. At each visit, participants will be asked by the study staff if they are experiencing any discomfort or symptoms that might indicate potential side effects of exenatide or NRT. Participants will be withdrawn from study participation if they show signs of serious adverse reactions that pose a threat to their physical or psychological health. Any symptoms or complaints, solicited or spontaneously reported, will be recorded and reported to the IRB and NIDA if events are classified as serious.

Data collection, entry and storage
Checklists will guide study personnel in all procedures for data collection and data management. Whenever possible, questionnaire data are entered directly into the computer by the participant, reducing data entry error. All neurobehavioal data are collected automatically by the computer using professional programs designed for this purpose and does not allow missing or impossible values. All hand-entered data (miscellaneous study forms) are initially reviewed by the study coordinator for general accuracy and completeness. They are then double entered in REDCap, with any inconsistencies examined and resolved. Data quality will be monitored continuously by the quality control manager and any problems detected will be discussed with the PIs. If necessary, retraining of data collectors will be conducted. Only investigators will have access to the data.

Data security and plan for protecting confidentiality
All data collected on paper forms will be stored in locked cabinets, while electronic data will be stored in REDCap database on a secure password-protected server maintained by the UTHHealth Medical School Information Technology Department. Individual participants and their research data will be identified by a unique study identification number (study ID). The study data entry and study management systems will be secured and password protected. The participants’ contact information will be securely stored for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by IRB and institutional regulations.

Data monitoring
The study PI and research team will monitor data on ongoing basis. In addition, a data safety and monitoring board (DSMB) will oversee the ongoing progress of the study. The board consists of two physicians, a psychologist and a biostatistician who are not affiliated with the study or the sponsor. Each member will provide written documentation attesting to absence of conflict of interest. The initial responsibility of the DSMB is to review and approve the initiation of the trial. Thereafter, DSMB evaluations will be conducted on the annual basis. On the study completion, the DSMB will perform end-of-study evaluation. An emergency meeting of the DSMB (open, closed or executive session) may be called at any time by the Chairperson should questions of patient safety arise.

Trial stopping rules
The trial may be suspended or prematurely terminated if there is sufficient reasonable cause. Circumstances that may warrant termination or suspension include, but are not limited to determination of unexpected, significant or unacceptable risk to participants; insufficient compliance to protocol requirements; and/or data that are not sufficiently complete and/or evaluable. If the study is suspended, it may resume once

concerns about safety, protocol compliance and data quality are addressed and satisfy the suspending party and the IRB.

Protocol modifications
The study PI will receive IRB approval before initiating any changes, including those required by the sponsor, which would affect study participants, such as changes in methods or procedures, numbers of kinds of the study participants, or revisions to the informed consent document or procedures. All protocol revisions will be submitted to the primary sponsor of research.

Project timeline
The recruitment for the study began on 7 December 2022, and the estimated primary completion date (final data collection for primary outcome measures) is 31 March 2026. It is anticipated that each site will recruit a minimum of 3 participants (6 participants between the two sites) per month for a total of 216 participants during the 36-month enrolment period. Once randomised, participant duration is 26 weeks.

Power calculation and sample size
Assumptions
Power considerations for the current trial were calculated to assess the effect of treatment on the primary outcomes in hypothesis 1 (4-week continuous abstinence) and hypothesis 2 (PCWG). Calculations were based on generating k=1000 normal approximations to the Bayesian posterior distribution via Monte Carlo simulation in the R Statistical Computing Environment. Statistical power was conceptualised as the percentage of the posterior distributions that met or exceeded a specific probability threshold (described below). All calculations assumed n=172 to account for 20% attrition. Regarding the placebo group effect size for NR T monotherapy (patch <22 mg) in hypothesis 1, the probability of abstinence was set to 0.305.61

Simulation results
Analyses will focus on posterior probabilities ≥0.70 that the effect of exenatide (relative to control) exists for both abstinence and weight. For hypothesis 1, given the assumptions above, calculations determined that the posterior probability met or exceeded 0.70 in 84.3% of simulations where an absolute difference in the probability of abstinence for control (0.305) was 10% lower than that for exenatide (0.405). For hypothesis 2, the same sample size met or exceeded the probability threshold in 84.3% of simulations when assuming a group difference in weight at the end of treatment as small as Cohen’s d=0.20. This study is thus powered to detect a posterior probability PP≥70% that exenatide confers at least 10% improvement in abstinence as well as a minimum effect size Cohen’s d=0.20 for lower weight at the end of treatment.

Statistical analysis plan
Descriptive statistics and confounding variables
Descriptive statistics will evaluate measures of central tendency and frequencies for all continuous and categorical variables (respectively) measured in the study. Preliminary data analyses will inspect relationships between sample characteristics, treatment condition and outcome variables via traditional statistical tests (eg, χ², Mann-Whitney; t-tests). Any sample characteristics that demonstrate a relationship with both treatment and the outcome variable in a given model meet criteria for being a potential confounder. Sample characteristics that will specifically be evaluated as potential confounders include sex, age, socioeconomic status, smoking heaviness and nicotine dependence, patch adherence, diet, physical activity, baseline BMI, and baseline weight concerns and weight efficacy. Any characteristic that meets the criteria as a potential confounder will result in two models: one with covariate adjustment for that characteristic and a simple model without adjustment. If adjustment does not affect inferences regarding the primary predictor-outcome relationship, the simple model will be retained. If the inferences change, we will report both models. All models will statistically control for the effect of site.

Inferential paradigm
Analyses will use Bayesian statistical inference to directly yield the probability of an alternative hypothesis given specified prior information. Weakly informative priors will be used as a default (eg, b ~N[µ=0,σ²=100]); for non-linear outcome variables this prior applies to the coefficient within the link-function). Sensitivity analyses using optimistic and pessimistic, sceptical priors will evaluate prior assumptions. Informative priors will use extant information (eg, meta-analytical findings61 for smoking outcomes). Analyses will use effective sample size and scale reduction factors to assess convergence.

Statistical modelling
Analyses will primarily use generalised linear modelling (GLM) with multilevel components (GLMM) for correlated observations. Multilevel models will incorporate random effects (eg, a level 2 intercept for correlated observations) as needed. Potentially non-linear relationships between predictors and outcomes will be evaluated via inclusion of polynomial or spline effects. Evaluation of distributional assumptions will use residual plots, formal statistical tests and posterior predictive checking. Violations of assumptions will be addressed via transformation, robust estimation, stratification and/or coefficient scaling where appropriate. GLM/GLMM will be performed using the R statistical computing environment via rstan and brms.

Missingness, multiplicity and secondary analyses
Intention-to-treat analyses
Will be conducted to provide estimates of treatment effects that are unbiased with respect to non-random drop
out. Individuals that drop out of the trial will be imputed as continuing to smoke. A per-protocol secondary analysis will provide an optimistic estimate of treatment effects. Missing data will be addressed via explicit modelling of missingness or imputation where appropriate. Each approach is robust to ignorable missingness (ie, missing completely at random (MCAR) and missing at random (MAR)). Sensitivity analyses will permit evaluation of the robustness of findings to missing data assumptions. Due to its observation of the likelihood principle,70 Bayesian analyses are less influenced by multiplicity; instead, all specified analyses are evaluated via a probability threshold of interest defined above. Secondary analyses will evaluate differences between abstainers and non-abstainers regarding all outcome variables, as well as potential interactions between treatment and baseline sample characteristics. Such analyses will retain the same probability threshold defined for the primary analyses, with exploratory credence given to higher thresholds.

**Specific analyses**

*Specific aim 1: hypothesis 1*

Compared with placebo, treatment with exenatide will result in a higher rate of 4-week continuous abstinence (self-reported and biochemically verified) at 12 weeks post-target quit day. GLM will evaluate 4-week continuous abstinence (yes vs no) as a function of treatment condition. Follow-up analyses will evaluate the trajectory of abstinence over time via GLMM.

*Specific aim 2: hypothesis 2*

Compared with placebo, treatment with exenatide will be associated with reduced PCWG at 12 weeks post-target quit day. GLM will evaluate residual change by modelling end of treatment weight as a function of treatment condition, controlling for baseline. GLMM will evaluate follow-up analyses of longitudinal changes in weight between groups over time.

*Exploratory aim 3: hypothesis 3a*

Compared with placebo, treatment with exenatide will result in a higher rate of 4-week continuous abstinence at 24 weeks post-target quit day. Analyses follow from those stated above for hypothesis 1, with the outcomes evaluated at 24 weeks post-target quit day instead of 12 weeks. GLM will evaluate 4-week continuous abstinence (yes vs no) as a function of treatment condition, and GLMM will evaluate the trajectory of abstinence over time.

*Exploratory aim 3: hypothesis 3b*

Compared with placebo, treatment with exenatide will be associated with a lower PCW at 24 weeks post-target quit day. Analyses follow from those stated above for hypothesis 2, with the outcomes evaluated at 24 weeks post-target quit day instead of 12 weeks. GLM will evaluate residual change by modelling treatment weight as a function of treatment condition, controlling for baseline, and GLMM will evaluate longitudinal changes in weight between groups over time.

*Exploratory aim 4: hypothesis 4*

Treatment with exenatide will be associated with an attenuation of ERP reactivity specific to nicotine-related and food-related stimuli at week 3 relative to baseline. Multivariate GLM will evaluate patterns of responses across different types of stimuli as a function of treatment group.

**Interim analyses**

Not applicable for this trial.

**Patient and public involvement**

None.

**Ethics and dissemination**

The study approval has been received from the UTHealth Committee for the Protection of Human Subjects (HSM-21-0639) and Baylor College of Medicine Institutional Review Board (H-50543). All participants will sign informed consent. The study is registered on ClinicalTrials.gov, NCT05610800. The study results will be disseminated via peer-reviewed publications and conference presentations.

**DISCUSSION**

Preclinical data showing that GLP-IRAs attenuate the reinforcing effects of food and nicotine, coupled with the results of the first human study that demonstrated the positive effects of exenatide treatment on smoking and weight outcomes, provide a strong premise for targeting GLP-1 receptors to facilitate smoking abstinence and mitigate PCW. Building on our previous 6-week trial of exenatide,25 the current study will include a longer, 14-week, treatment duration and a post-treatment follow-up at 12 weeks after the end of treatment. In addition to examining the impact of exenatide on smoking abstinence and PCWG, this trial will explore putative mechanisms by which exenatide might modulate smoking and weight outcomes. The most compelling preclinical evidence to date suggests attenuation of responding in brain networks related to reward processing as a plausible mechanism of action. By measuring ERP reactivity to nicotine-related and food-related stimuli, we aim to interrogate reward-relevant cortical regions by which exenatide might reduce smoking and mitigate PCWG.

We note three key limitations of this study. First, the trial’s focus on individuals with pre-diabetes and/or overweight may limit the generalisability of the findings. Second, administration of the study medication during in-clinic visits will not allow assessment of acceptability and adherence to a subcutaneously administered therapy for smoking cessation and weight management in the real world. Third, the 14-week treatment duration and the 12-week post-end-of-treatment follow-up periods are relatively short. If the hypotheses of this study are confirmed, subsequent research would require examination of exenatide over a longer treatment period and a post-treatment
follow-up to ascertain the optimal length of therapy and the sustainability of exenatide’s effects.

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Contributors According to the definition given by the International Committee of Medical Journal Editors, all the authors qualify for authorship. LY designed the study and wrote the first draft of the study protocol. CDV, FV and JS made substantial contributions to the overall study design. FV and HEW designed the EEG paradigm. PMC developed the smoking cessation counselling protocol. RS undertook the statistical power calculation and statistical analysis plan. LW wrote the first draft of the manuscript based on the study protocol. CDV, FV, MSW, TK, HA, SBL and JS contributed with manuscript revisions and important intellectual content. All authors have approved the final manuscript.

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Informed Consent: Exenatide for Smoking Cessation and Prevention of Weight Gain

CONSENT TO TAKE PART IN RESEARCH

Simple Study Title: Exenatide for Smoking Cessation and Prevention of Weight Gain

Full Study Title: A Randomized Controlled Trial of Exenatide as an Adjunct to Nicotine Patch for Smoking Cessation and Prevention of Post-Cessation Weight Gain

Study Sponsor: National Institutes of Health, National Institute of Drug Abuse

Protocol No.: HSC-M5-21-0639

Principal Investigators: Luba Yammine, PhD
CNRA, Faillace Department of Psychiatry & Behavioral Sciences, UTHealth

Christopher Verrico, PhD
Baylor College of Medicine, Michael E. DeBakey VA Medical Center

Study Contact: Jessica Vincent, QA Manager and Study Coordinator, 713-486-2803

You are invited to take part in this research study. This consent form has important information about this study to help you decide whether or not to take part in this study. Your decision to participate is voluntary. You may refuse to take part, or choose to stop taking part, at any time. A decision not to take part or to stop being a part of the research project will not change the services available to you from Dr. Luba Yammine or the research staff at the University of Texas Health Science Center at Houston (UTHealth).

The purpose of this study will examine whether a medication called exenatide (Bydureon) is useful as a treatment for people who want to quit smoking and prevent post-quit weight gain. Exenatide is not available for this purpose outside of study because it is experimental and not approved for this purpose. Exenatide is thought to influence certain chemicals in your brain that affect craving for both cigarettes and food.

If you choose to participate in this study, you will be asked to complete an intake evaluation at UTHealth Center for Neurobehavioral Research on Addiction (CNRA) to determine your eligibility for the study. This intake process will involve medical and psychiatric evaluations by trained clinical staff members. If you qualify for the study, you will begin 14 weeks of outpatient treatment at the Treatment Research Clinic of the CNRA. The treatment will focus on helping you stop smoking. Once a week, you will be given the study medication, extended-release exenatide, also known as Bydureon or placebo (an inactive substance like saline). You will also receive nicotine patches for daily use and individual smoking cessation counseling. Exenatide (Bydureon) is approved for the treatment of type 2 diabetes. It is an injectable medication that is given just under the surface of the skin. Medical staff at the CNRA will take your vital signs and check your blood sugar level using a finger-stick procedure. You will also be asked questions to learn about any changes in cigarette smoking, cravings for cigarettes and food, and how you are feeling in general. Following completion of the 14-week treatment, you will be asked to come in for two follow-up visits (week 15 and week 26). The total amount of time you will be in this study is 27 weeks.

There are potential risks involved with this study that are described in this document. Some known risks include potential medication side effects, injection-site reactions, or discomfort answering personal questions.

There are potential benefits from your participation in this study. The study could help you quit smoking cigarettes while controlling your weight, and the information gained from your participation may benefit others in the future.

If you do not want to be in the study, there are no other choices except not to take part in the study, but researchers will provide you with referrals to other treatment programs in the community.

If you are interested in participating, please continue to read below.
What is the purpose of this study?
The purpose of this study is to investigate a potential treatment for quitting smoking and preventing post-quit weight gain.

This study will involve administration of exenatide (Bydureon), which is approved by the Food and Drug Administration (FDA) for the treatment of diabetes but not approved for treating nicotine addiction or weight maintenance. Because of this, exenatide is considered an "experimental" drug in this study. The sponsor is paying for this study to be completed.

A description of this clinical trial will be available on http://www.clinicaltrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

Who is being asked to take part in this study?
You have been invited to join this research study because you have elevated blood sugar (prediabetes) or are overweight and you are a cigarette smoker who wants to stop smoking. The study will enroll a total of 216 participants at two locations: the University of Texas Health Science Center at Houston (UTHealth) Center for Neurobehavioral Research on Addiction (CNRA) and Baylor College of Medicine (BCM), Michael E. DeBakey VA Medical Center (MEDVAMC).

What will happen if I take part in this study?
If you agree to participate in this study, we will perform a screening procedure to determine your eligibility. The screening will involve answering questions regarding your demographic and health history, lifestyle habits, a urine test to confirm that you are a smoker and rule out illicit drug use, and providing a blood sample (about 2 tsp of blood) for laboratory analysis. You will have your medical and psychiatric history taken, and a physical exam will be performed. You will be asked for your name, address, phone number, email address, and date of birth. The screening visit will take about 2 hours.

If you are determined eligible to participate in this study, you will have to return for 14 weekly visits (with one week separating each two visits). In addition, you will have to return for follow-up visits at week 15 and week 26. Visits 1 (week 1) and 3 (week 3) will take about 1.5 hours. The rest of the visits will take 35-45 minutes. You should not consume alcohol prior to any study visit, nor are any illicit (illegal) drugs permitted during any time while on study. If you take any over-the-counter (OTC) or prescription medications, the study principal investigator (PI) will review them and discuss with you whether these are allowed while you are in the study.

As part of this study you will receive a medication called exenatide (Bydureon) or you will receive placebo (an inactive substance like saline). You will not know which medication you will receive. You will receive exenatide or placebo by injection at each of your clinic visit during weeks 1-14. Regardless of whether you receive exenatide or placebo, you will also receive nicotine replacement therapy (nicotine patches) for daily use and weekly smoking cessation counseling during weeks 1-14. Your target quit date will be two weeks after the start of the study (after you have received two doses of the exenatide or placebo). You should do your best to entirely abstain from smoking after your target quit date; however, if you relapse, you will still be able to continue the study and try to quit later during the study. Your smoking status will be biochemically verified during each visit using breath test.

This treatment portion of the study will take 14 weeks in total, requiring you to come in once a week for a total of 14 visits. The following will occur during each study visit (weeks 1-14):

- Your blood pressure, heart rate, respiratory rate, weight, smoking status (using self-report and breath test), fingerstick stick blood sugar levels, health status, and overall wellbeing will be assessed.
- You will be asked to complete several questionnaires.
- You will receive exenatide or placebo. Exenatide/placebo is administered subcutaneously (in the fatty tissue) in the back of your arm, stomach or thigh area. The medication can be administered with or without food.
- You will receive a 1-week supply of nicotine replacement therapy (nicotine patches) for the upcoming week and individual smoking cessation counseling. Smoking cessation counseling will address preparation for quitting, identification of high-risk situations for smoking, support before and after the quit date, management of withdrawal symptoms, and keeping or resetting a quit date.
Informed Consent: Exenatide for Smoking Cessation and Prevention of Weight Gain

If you are a woman of childbearing potential, you will be asked to complete a urine pregnancy test every two weeks.

In addition to the procedures described above, during week 1 and week 3 visits, the study staff will record your brain activity using an encephalogram (EEG, please see the details below).

Following the treatment completion, you will be required to return to clinic two times (follow-up visits), at week 15 and at week 26, for the assessment of smoking status (using self-report and breath test), weight and waist circumference and completion of several questionnaires. In addition, a blood sample (about 2 tsp of blood) for laboratory analysis will be collected during the week 15 and week 26 follow-up visits.

EEG. EEG will be conducted during week 1 and week 3 visits. To record your EEG, a net-like cap will be placed on your scalp. While you are wearing the cap, you will be asked to look at a series of pictures on a screen in front of you, and you may or may not be asked to perform a decision-making task. You may be offered a small snack (such as a granola bar, crackers, or similar) before the EEG, in which case, the study staff will ask you about any food allergies you may have. The pictures will include images of people, nature scenes, artwork, food and/or nicotine related content, and images that may be disturbing (such as mutilated bodies or nude people). You will be shown examples of these pictures before you start this part of the visit. After you complete the EEG, you may be asked to view and rate a set of pictures that are similar to the ones you viewed during the EEG. These pictures are images that have been used in other studies. Obtaining ratings from many people will help to validate these pictures for use in this type of research. You may also be asked to complete a short computer task called Mouse Tracking. For this task, you will use a computer mouse to click on pictures and objects on the screen. This will take about 10 minutes to complete. Finally, you will be asked to complete a short survey to provide feedback about the study session. This should take about 5 minutes to complete. A camera will be used to monitor you during the session. No videos or images will be recorded during the session.

How long will you be in the study?
If you agree to take part, your participation will last for about 27 weeks (17 visits total) and will involve 1 visit for the screening procedures, 14 weekly clinic visits (weeks 1-14) during the treatment part of the study, and 2 follow-up visits (week 15 and week 26).

What choices do you have other than this study?
You may select other options than being in this research study. The research staff will be happy to discuss these other options with you if you choose not to take part in this study.

What are the risks of taking part in this study?
There are both risks and benefits to taking part in this study. It is important for you to think carefully about these as you make your decision.

Risks of exenatide: Extended-release exenatide (Bydureon) has the following Black Box Warning:

Risk of Thyroid C-Cell Tumors
- Exenatide extended-release (Bydureon) causes thyroid C-cell tumors at clinically relevant exposures in rats. It is unknown whether Bydureon causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC) in humans, as human relevance could not be determined by clinical or nonclinical studies.
- Bydureon is contraindicated in patients with a personal or family history of MTC or in patients with multiple endocrine neoplasia type 2.

There is a risk that you could have side effects from the study medication (Bydureon).

Common side effects associated with exenatide (Bydureon) include nausea, diarrhea, injection site nodule (a bump at the injection site), constipation, headache, dyspepsia (indigestion), vomiting, and injection site reaction. A regular reaction site reaction consists of swelling and discomfort at the injection site. A severe injection site reaction (described below) is more serious and consists of damage to the tissue.
The risk of low blood sugar (hypoglycemia) with the use of exenatide is low. However, the risk of getting low blood sugar may be higher if exenatide is combined with another medicine that can cause low blood sugar (i.e. insulin). Upon the study entry and during the course of the study, the investigators will ask you about all medications that you are taking. Signs and symptoms of low blood sugar include dizziness or lightheadedness, sweating, confusion or drowsiness, headache, blurred vision, slurred speech, Shakiness, fast heartbeat, anxiety, irritability, mood changes, hunger, weakness, or feeling jittery.

Other serious reactions include hypersensitivity reaction (an exaggerated reaction to the medicine), anaphylaxis (life threatening allergic reaction), nephrotoxicity (poisonous effect on the kidneys), pancreatitis (inflammation in the pancreas), decreased platelet count (i.e. reduced number of platelets in your blood) and severe injection site reaction (severe pain, swelling, blisters, or a dark scab). In studies of patients without diabetes, the most common side effect of exenatide treatment was nausea. Overall, the side effects of exenatide are similar among patients with and without diabetes.

You will be asked if you have been experiencing various symptoms such as nausea, indigestion, stomach pain, diarrhea, changes in urination, weakness and other symptoms. Certain symptoms may prompt further evaluation by medical personnel and collection of blood samples for laboratory analysis. You will also meet with a study doctor at each injection visit and be checked for any symptoms or side effects.

Pregnancy: Exenatide (Bydureon) may harm your unborn baby. If you are a woman of childbearing potential (being able to become pregnant), due to the possible risks to a fetus, you may not participate in this study unless you are not pregnant and, with the investigator’s knowledge and approval, you are using a medically acceptable form of birth control (contraception). Examples of reliable forms of birth control include the Pill, Norplant, Depo-Provera, and consistent and correct use of condoms. You must agree to give urine samples to test for pregnancy (at no charge to you) before entering the study and during the study.

Other potential risks include -

Risks of nicotine replacement therapy: Nicotine patches is an OTC product with a proven safety record. Common side effects associated with nicotine patches include skin irritation, itchiness, rapid heartbeat, dizziness, and nausea.

Risks of blood collection: The risks of inserting a needle into a vein may involve pain from insertion of the needle; lightheadedness; fainting; hematoma (like a bruise) at the site of the needle insertion; inflammation of the vein; clotting of the vein; rarely, infection where the needle enters the skin, or rarely, an allergic reaction to the tape applied afterwards.

Risks of subcutaneous injection: The risks of subcutaneous injection may include pain from insertion of the needle, injection site reaction (i.e., abscess, cellulitis, or necrosis) with or without a nodule, or rarely, an allergic reaction to the tape applied afterwards.

EEG: Having an EEG may lead to skin irritation where the sensors are placed on the scalp. In addition, questionnaires may contain questions that are sensitive in nature. You may refuse to answer any questions that makes you feel uncomfortable. In the unlikely event that you become distressed from viewing certain images during the study or remain distressed after the study, mental health professionals are available for you to meet with.

Confidentiality: There is a risk of loss of confidentiality. In order to maintain confidentiality, all information you will provide in this study will not be provided to anyone outside the research group unless you give us written permission to do so. The only exceptions to this are reports of child abuse, elder abuse, or if you have serious thoughts to harm yourself or others.

Unknown Risks: There may be some risks that the study doctors do not yet know about.

What are the benefits to taking part in this study?
The benefits of participating in this study may be smoking cessation and prevention of post-cessation weight gain. However, you may receive no direct benefit from participating.

The study may help the study doctors learn things that may help others in the future.
Can you stop taking part in this study?
Your participation in this study is voluntary. You may decide to stop taking part in the study at any time. To withdraw from the study, please contact Dr. Luba Yammine at 713-486-2800.

Your doctor or the sponsor can stop the study at any time. Your doctor or the sponsor may stop your participation in the study if your condition worsens, the study is stopped, the study medication is no longer available, you do not meet all the requirements of the study, or the study is not in your best interest. If your participation in the study is stopped, your doctor will discuss other options for your treatment.

If you stop participating in this study, the information already collected about you will still be used in the data analysis. However, no further information will be collected without your permission.

While taking part in this study, the study team will notify you of new information that may become available and could affect your willingness to stay in the study.

What happens if you are injured during the study?
In the event of injury resulting from this research, UTHealth is not able to offer financial compensation nor to absorb the costs of medical treatment. However, necessary facilities, emergency treatment, and professional services will be available to you, just as they are to the general community. You or your insurance company will be billed for any treatment. You should report any such injury to Luba Yammine at 713-486-2800 and to the Committee for the Protection of Human Subjects at 713-500-7943. You will not give up any of your legal rights by signing this consent form.

What are the costs of taking part in this study?
There are no costs to you to participate in this study. If you receive a bill that you believe is related to your taking part in this research study, please contact Dr. Yammine at 713-486-2800 with any questions.

Will you receive compensation for taking part in this study?
You will receive compensation for participating in this study as follows:
- Screening = $20
- Week 1-4 visits = $10/visit
- Week 5-8 visits = $15/visit
- Week 9-12 visits = $20/visit
- Week 13-14 visits = $25/visit
- Week 15 follow-up visit = $30
- Week 26 follow-up visit = $50
- EEG sessions (week 1 and week 3) = $20/session
- Return of used/unused nicotine patches (weeks 2-15) = $5/weekly return
- Additional coverage as needed for transportation-related expenses (e.g., bus, parking).

The total amount of compensation, including the screen, 14 treatment visits, follow-up visits at weeks 15 and 26, nicotine patch returns, and two EEG sessions will be $440.00.

You will be compensated with cash or a cash equivalent (reloadable debit card or gift cards), following the completion of each study visit. All information is stored in a secure fashion and will be deleted from the system once the study has been completed.

If you receive payment for taking part in this study, please be informed that you will be asked to complete a copy W-9 form that will be forwarded to the accounting department as a requirement by the Internal Revenue Service. You will also be issued a 1099-Misc form from this study for tax reporting purposes.

IRB NUMBER: HSC-MS-21-0639
IRB APPROVAL DATE: 08/23/2021
Informed Consent: Exenatide for Smoking Cessation and Prevention of Weight Gain

The University of Texas Health Science Center at Houston owns any data collected and the use of the data, results, treatments, or inventions that can be made from the research. The University’s ownership includes the right to license or transfer the use or ownership to other parties including without limitation, commercial entities contracting with UTHealth. There are no plans to compensate you for any patents or discoveries that may result from your participation in this research study. You will not be paid for any use of your data, samples, or results.

How will privacy and confidentiality be protected?
Your privacy is important and your participation in this study will be kept confidential. However, absolute confidentiality cannot be guaranteed.

If you sign this document, you give permission to UTHealth to use and disclose (release) your health information. The health information that we may use or disclose for this research includes medical history and psychological testing information obtained at intake screening. Please understand that health information used and disclosed may include information relating to HIV infection, drug abuse, alcohol abuse, behavioral health, and psychiatric care.

Personal identifiers such as your name and medical record number will be removed from the information and samples collected in this study. After we remove all identifiers, the information or samples may be used for future research or shared with other researchers without your additional informed consent.

Please understand that research study data will be sent to the sponsor of this research study, National Institutes of Health (NIH). The data that will be sent to the sponsor will not include your name but may include your initials, date of birth, date of study visits, and date of study procedures.

People who receive your health information may not be required by Federal privacy laws (such as the Privacy Rule) to protect your health information and may share your information with others without your permission, if permitted by laws governing them. You will not be personally identified in any reports or publications that may result from this study. If all information that does or can identify you is removed from your health information, the remaining information will no longer be subject to this authorization and may be used or disclosed for other purposes.

Representatives of the organizations listed below will see your name and other personal identifiers when they review your research records and medical records for the purposes of verifying study data:
- Representatives of UTHealth
- Representatives from the U.S. Food and Drug Administration (FDA)
- Representatives from the National Institute on Drug Abuse (NIDA)
- Members of Data and Safety Monitoring Boards (an independent group of experts that reviews this study’s data to make sure participants are safe and the research data is reliable)
- Companies engaged with UTHealth for the commercialization of the results of the research study

Please note that you do not have to sign this Authorization, but if you do not, you may not participate in this research study. UTHealth may not withhold treatment or refuse treating you if you do not sign this Authorization.

You may change your mind and revoke (take back) this Authorization at any time. Even if you revoke this Authorization, researchers may still use or disclose health information they already have obtained about you as necessary to maintain the integrity or reliability of the current research. To revoke this Authorization, you must contact Dr. Luba Yammine in writing at 1941 East Road, Houston, TX. 77054.

This Authorization will expire 15 years after the end of the study.

Certificate of Confidentiality:
To help us protect your privacy, we have obtained a Certificate of Confidentiality from the National Institutes of Health. With this Certificate, the researchers cannot be forced to disclose information that may identify you, even by a court subpoena, in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings. The researchers will use the Certificate to resist any demands for information that would identify you, except as explained below.

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The Certificate cannot be used to resist a demand for information from personnel of the United States Government that is used for auditing or evaluation of federally funded projects or for information that must be disclosed in order to meet the requirements of the federal Food and Drug Administration (FDA).

You should understand that a Certificate of Confidentiality does not prevent you or a member of your family from voluntarily releasing information about yourself or your involvement in this research. If an insurer, medical care provider, or other person obtains your written consent to receive research information, then the researchers will not use the Certificate to withhold that information.

The Certificate of Confidentiality does not prevent the researchers from disclosing, without your consent, information that they are required by law to disclose to government authorities. For example, researchers must comply with laws requiring the reporting of suspected child abuse and neglect and communicable diseases.

Whom can you contact if you have questions about the study?
If you have questions at any time about this research study, please feel free to contact the principal investigator, Dr. Luba Yammine at 713-486-2800, as they will be glad to answer your questions. You can contact the study team to discuss problems, report injuries, voice concerns, obtain information in addition to asking questions about the research.

The Committee for Protection of Human Subjects at the University of Texas Health Science Center has reviewed this research study. You may contact them for any questions about your rights as a research subject, and to discuss any concerns, comments, or complaints about taking part in a research study at (713) 500-7943.

SIGNATURES
Sign below only if you understand the information given to you about the research and you choose to take part in this research study. Make sure that all your questions have been answered. If you decide to take part in this research study, a copy of this signed consent form will be given to you.

Printed Name of Subject ______________________ Signature of Subject ______________________ Date __________ Time __________

Printed Name of Person Obtaining Informed Consent ______________________ Signature of Person Obtaining Informed Consent ______________________ Date __________ Time __________

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