Protocol Title	Impact of sugars on tobacco product toxicity and abuse liability
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PROTOCOL COVER PAGE

REVISION HISTORY

Revision #	Version Date	Summary of Changes	Consent Change?
1	15 NOV 2021	Revised screening process	Y
2	19 JAN 2022	Updated inclusion criteria, added additional MNWS survey	N
3	26 JUL 2022	Revised inclusion criteria (CPD)	N
4	22 FEB 2023	Revised exclusion criteria (Marijuana use), revised recruitment target (N from 30 to 25)	N
5	01 DEC 2023	Revised screened number and increased N to 30 account for data collection oversights with early completers. Added language clarifying CTSI monitoring oversight and study cigarette storage temperatures.	N

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ABBREVIATIONS/DEFINITIONS

- AE: Adverse Event
- CES-D: Centers for Epidemiological Studies 20-item scale
- DAST: Drug Abuse Screening Test
- FTND: Fagerstrom Test for Nicotine Dependence
- HPHC: Harmful and Potentially Harmful Constituents
- IUD: Intrauterine Device
- IVRS/IVR: Interactive Voice Response System
- MAST: Michigan Alcohol Screening Test (Short form)
- SAE: Serious Adverse Event
- UB: Usual Brand

1.0 Objectives

To investigate a comprehensive set of abuse liability and appeal measures, smoking intensity, as well as analyze the impact of sugar content on the formation of DNA adducts derived from aldehydes and oxidative stress in the oral cavity of smokers.

2.0 Background

Chemical constituents of tobacco and cigarette smoke play crucial role in addictiveness, toxicity and carcinogenicity of tobacco products. The U.S. FDA established a list of 93 harmful and potentially harmful constituents (HPHC) in tobacco and cigarette smoke that cause or have potential to cause these and other harmful effects.[1] Levels of many HPHCs in cigarette smoke can be substantially reduced by modifying cigarette manufacturing approaches.[2] However, in the absence of regulation, smokers are being exposed to variable and often unnecessarily high levels of such constituents. According to the Family Smoking Prevention and Tobacco Control Act, the FDA can set standards for HPHCs.[3] Such regulation is likely to serve as a powerful tool in efforts to protect public health. As an example, reduction of nicotine in cigarette tobacco can reduce abuse liability of cigarettes.[4] In addition, prospective epidemiological studies have shown that the level of intake of some tobacco carcinogens is predictive of the risk of cancer development in smokers, suggesting that limiting smokers' exposures to such constituents may be beneficial.[5-7] Therefore, imposing standards for constituents that contribute to addictive and toxic properties of cigarette smoke can potentially help to reduce smoking prevalence and/or minimize harmful exposures in smokers who are unable or unwilling to quit.

Soluble sugars such as sucrose, fructose, glucose are formed via enzymatic hydrolysis of starch in tobacco material during its processing, and are also added to tobacco blend during cigarette manufacturing.[8] Tobacco manufacturers also use a variety of other sugar-containing ingredients such as brown sugar, honey, corn syrup, and molasses.[8, 9] During cigarette combustion, processes such as Maillard reactions and sugar caramelization and pyrolysis can result in the formation of a variety of products (Figure 1), including aldehydes (e.g., formaldehyde, acetaldehyde, acrolein), furans (e.g., 2,5-dimethylfuran, furfural and 5-hydroxymethylfurfural), other volatile compounds (e.g., benzene, acrylamide, polycyclic aromatic hydrocarbons), ketones (e.g. diacetyl), and acids (e.g., formic and acetic acid). Therefore, sugars in tobacco filler are likely to have a profound impact on cigarette smoke properties. First, the majority of the products of sugar decomposition are important *toxicants and carcinogens*.[10-18,21] In addition, some volatile products of caramelization and acids formed during sugar pyrolysis play an important role in *palatability-related smoke*

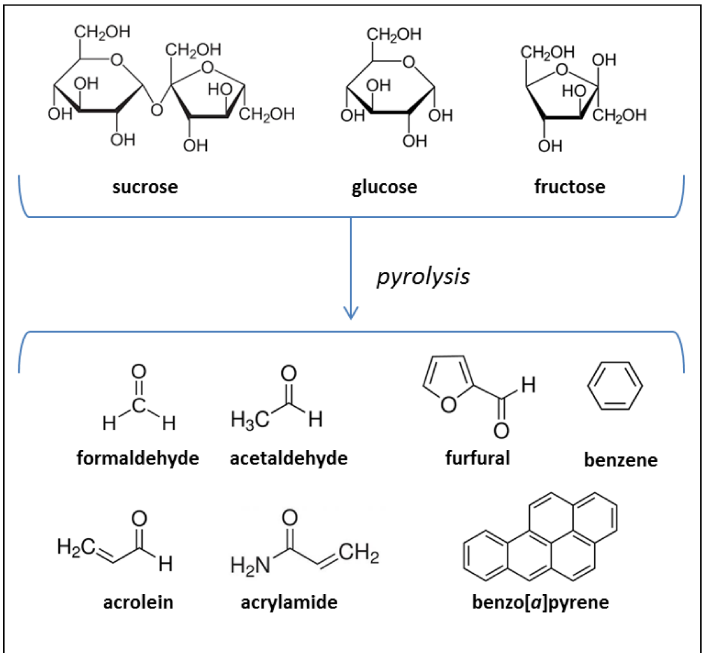

Figure 1. Some of the products of sugar pyrolysis discussed in this proposal.

characteristics such as flavor, taste, and harshness. Flavor and taste can be influenced by diacetyl and other products of Maillard reaction (and subsequent Amadori rearrangement) and caramelization.[8] Acetic acid and formic acid, the most abundant pyrolytic products of sugars, can contribute to palatability of smoke by lowering its pH and reducing its harshness. This is particularly important for American blended cigarettes which contain Burley tobacco that yields harsh smoke with high pH.[22, 23] Indeed, tobacco manufacturers are using various sugars as casings with the purpose of balancing and enhancing these sensory qualities and developing specific taste and flavor characteristics for cigarette brands.[22-24] Lastly, acetaldehyde and potentially other products of sugar decomposition may contribute to *addictiveness* of cigarette smoke. For example, acetaldehyde increases dopaminergic neuronal activity and enhance nicotine self-administration in laboratory animal studies.[25, 26]

For a tobacco constituent to be considered for potential regulation, it is important that there are known approaches to its control and/or reduction in tobacco products. American blended cigarettes typically contain a mixture of tobaccos cured by different methods; therefore, levels of "natural" sugars in tobacco filler can be reduced by adjusting tobacco blending and processing practices. For example, it is known that curing tobacco at elevated temperatures prevents sugar metabolism and results in higher sugar content in tobacco: 8-30% of tobacco weight in flue-cured Virginia tobacco and 10-20% in sun-cured Oriental tobacco. In contrast, processed Burley tobacco is low in sugars (<0.2%) because it is subjected to air-curing, a slow processing method which allows sugars to be metabolized through enzymatic processes.[22, 27] Compensation for such losses is one of the main reasons why manufacturers add sugars in cigarette manufacturing. Ban on added sugars is another, obvious approach to sugar content reduction in tobacco filler.

To summarize, as precursors to smoke constituents that play important roles in smoke toxicity, carcinogenicity, palatability, and addictiveness, *sugars are likely the most versatile key constituents contributing to the smoking-associated morbidity and mortality*. Manufacturer reporting of sugar levels in tobacco products could be required by the FDA if sugars are added to HPHC list, which would allow for a more accurate characterization of harmful potential of cigarettes and other combustible or heated tobacco products. Furthermore, reductions of sugar content in cigarette tobacco could potentially result in decreased palatability of cigarette smoke, make it harder to inhale due to increased harshness, and reduce levels of certain volatile toxicants and carcinogens.

3.0 Study Endpoints/Events/Outcomes

3.1 Primary Endpoint/Event/Outcome

To evaluate the impact of sugar content on smoking intensity (nicotine levels in spent filters), subjective responses to cigarettes (e.g., reinforcing and sensory effects) and behavioral measures (multiple choice procedure, cigarette purchase task). We hypothesize that the collected measures will indicate lower abuse liability for cigarettes with lowest sugar content.

3.2 Secondary Endpoint(s)/Event(s)/Outcome(s)

To conduct an exploratory analysis of the relationship between sugar content in study cigarettes and levels of aldehyde- DNA adducts in oral cells of study participants after smoking these cigarettes. Aldehydes are known to cause respiratory tumors in laboratory animals and DNA adducts in the human lung[10,11,14]

4.0 Study Intervention(s)/Investigational Agent(s)

4.1 Description of study cigarettes

Winston brand cigarettes will be modified by adding a mixture of sucrose to each cigarette at 2 levels so that the amount of total (originally present and added) sugar content in these cigarettes matches median and highest levels found in popular brands analyzed in Aim 2. For example, median and highest levels of the sum of sucrose, glucose, and fructose in the CDC publication were 5.7% and 8.9% (w/w), respectively, across the 20 unidentified brands.[50] The brand #19 in that study has the lowest sum of these sugars at 3.3% w/w. This allows for addition of sucrose to this brand at 2.4% and 5.6% w/w to achieve median and highest levels in that study. We will use similar calculations to determine the amount of sugars to be added to study cigarettes in this laboratory study.

Medicinal-grade ultrapure sucrose manufactured under GMP standards will be used for the modification of Winston cigarettes. The prepared cigarettes will be conditioned at 25 °C and 60% relative humidity for 2 days, and then stored at 4 °C until their use in study procedures. We used this approach in our previous studies in which we added NNK to cigarettes that were smoked by study participants under the FDA Center for Tobacco Products Protocol Number P00006.

4.2 Handling of Study Cigarettes

The finished study cigarette product will be packaged by the Stepanov laboratory in sterilized tins containing 3 (1 extra) cigarettes with a label that encodes the level of sugar content, which will remain blind to the study investigators. The tins will be transported to the research clinic. The number of cigarettes transported from the laboratory to the clinic will be recorded at the lab and then at the clinic upon receipt. At the clinic, the cigarettes will be refrigerated until their use at 4 degrees Celsius. Any temperature variations over +/- 3 degrees C will be discussed with PI to determine if the product freshness has been impacted. Upon participant randomization, the appropriate tin with a specified label will be pulled from the refrigerator. The label on the tin will be put in the participant's case report book and recorded on the product distribution log. All unused cigarettes will be destroyed and disposed of.

4.3 **Biosafety**: NA

4.4 **Stem Cells**: NA

4.5 **Fetal Tissue**: NA

5.0 Procedures Involved

5.1 Study Design

Overview: Participants (N=30 completers) will complete a baseline visit where they will smoke their usual brand cigarette. In the next three sessions, they will receive one of three study cigarettes with varying sugar content (low, medium and high) in a double-blind manner and counterbalanced order across participants. In each session, participants will first smoke either their usual brand cigarettes (at baseline) or their assigned study cigarette (subsequent sessions) in a regimented manner: 10 puffs total, 30 seconds between puffs. There will be a one-hour interval since the time of cigarette extinction before smoking the next cigarette. After this interval, participants will smoke their assigned cigarette ad libitum within a 10 minute time period. Safety and subjective measures will take place during this session as described below.

Anticipating a 60-65% attrition rate based on current experiences, we will recruit up to 75 participants.

Study Procedures: Smokers who smoke at least 5 cigarettes/day will attend 4 laboratory sessions during which they will be asked to smoke their usual brand (UB) cigarettes and then one of three study cigarettes with low, medium and high levels of sugar in separate sessions using a within-subject design with conditions counterbalanced determined by a Latin square. In each session, smokers will be asked to smoke a cigarette in a standardized manner (10 puffs, 30 second interval between puffs) and 1 hour later, *ad libitum*. Each of the sessions will be separated by at least 48 hours but not more than 5 days. The proposed study design has been used to assess the abuse liability of electronic cigarettes compared to other tobacco/nicotine products,[99-101] that vary in flavors and modified risk claims,[102] and that vary in menthol

concentration and nicotine dose.[103] This design is also being utilized to determine the abuse liability of flavored cigar products.[104]

Cigarette smokers (n=30 completers) will be recruited from advertisements through a variety of media outlets, flyers and the internet. Interested cigarette smokers will contact the University of Minnesota Tobacco Research Programs, be informed about the study and initially screened for eligibility over the telephone or HIPAA compliant website. Subjects who pass initial screening will then be asked to attend a screening visit during which the study will be explained in detail, informed consent will be obtained and the screening questionnaires and procedures will be completed to confirm eligibility. Screening procedures include: Tobacco Use History and Exposure; Fagerstrom Test for Nicotine Dependence (FTND);[105] Wisconsin Index of Smoking Dependence Motives[146]; Demographics; Medical History and Current Health Status; Concomitant Medications Questionnaire; Prime MD;[106] Centers for Epidemiological Studies 20-item scale (CES-D);[107] Michigan Alcohol Screening Test (MAST) Short form;[108] Drug Abuse Screening Test (DAST). [109]

Eligible participants will be asked to attend a baseline visit in the clinic. Blood pressure and heart rate will be assessed. Confirmation of smoking status will be done using a portable CO device and or a urine sample (NicCheck strip). A urine sample will also be collected to determine pregnancy status for women of childbearing potential. At the end of the baseline visit we will train participants on how to use our Interactive Voice Response System (IVRS). Participants will undergo one week of baseline measurement. Daily surveys will be completed in the IVR to assess frequency of cigarette smoking and other tobacco and marijuana use. This will provide an accurate assessment of whether or not our participants meet the eligibility criteria for smoking and an assessment of potential confounding factors. At the end of this one-week period, participants will be asked to attend 4-half day long laboratory sessions, during which 2 cigarettes (fixed puffing pattern and then *ad libitum*) will be smoked and assessments will be made (Figure 2). Daily IVR surveys will continue until the end of the study.

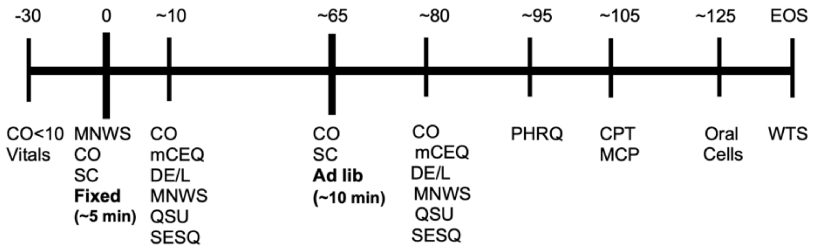

Figure 2: Laboratory measures and procedures

Session timeline in minutes. MNWS: Minnesota Nicotine Withdrawal Scale; CO: expired air carbon monoxide; SC: study cigarette; Fixed: 10 puffs (1puff/30 seconds) of session cigarette administered; mCEQ: Modified Cigarette Evaluation Questionnaire; DE/L: Drug Effects/Liking Questionnaire; QSU: Questionnaire of Smoking Urges-Brief; SESQ: Sensory Effects of Smoking Questionnaire; PHRQ: Perceived Health Risk Questionnaire; CPT: Cigarette Purchase Task; MCP: Multiple Choice Procedure; WTS: Willingness to Switch; EOS: End of session.

The first session for all participants will involve smoking their UB cigarettes. Participants will be asked to refrain from smoking for at least 12 hours prior to each session and must have alveolar CO ≤ 10 ppm to qualify for the session. Subsequently, the IVR records will be examined and vitals (blood pressure and heart rate) will be assessed through an automated cuff to ensure that eligibility criteria are still met. After a 30-minute rest period, participants will complete the MNWS, submit an alveolar CO sample, and will smoke their UB cigarettes in a regimented manner (10 puffs total, 30 seconds between puffs). Five minutes after extinguishing the cigarette, another CO measurement will be taken and participants will be asked to complete the mCEQ, Drug Effects/Liking Questionnaire, MNWS, QSU and Sensory Effects of Smoking Questionnaire, in a specified order via REDCap. The spent cigarette filter will be collected for nicotine analysis. There will be a one- hour interval since the time of cigarette extinction before smoking the next cigarette. During the intervening times between cigarettes, smokers will be allowed to read magazines, listen to neutral podcasts, or watch neutral videos. After this interval, participants will submit another CO, complete the MNWS and smoke their UB cigarettes *ad libitum* within a 10-minute timeframe and the same testing procedures will be followed. Twenty minutes after the second cigarette, the Perceived Health Risk Questionnaire will be administered and then at 30 minutes the Cigarette Purchase Task and Multiple Choice Procedures for the UB cigarettes will be administered. At 50 minutes (2 hours after smoking the first cigarette), participants will be asked to rinse their mouths and oral cells will be collected. At the very end of the session, the Willingness to Switch questionnaire will be administered. Once the Willingness to Switch questionnaire has been completed a number will randomly be selected from the Multiple Choice Procedures task. This will be done by pulling a number 1- 16 out of a jar. The participants will receive either an additional cigarette or the money associated with that number, depending on which choice was made for that number. The participant may choose to smoke the cigarette or not.

In the next three sessions, participants will then be asked to smoke one of three study cigarettes with varying sugar content in a double-blind and counterbalanced order across participant s. Each study cigarette type will be labeled with a symbol (diamond, square or star to minimize ranking bias). Blinding of the cigarettes will occur in Dr. Irina Stepanov's laboratory, where staff do not have contact with participants. The same procedures as implemented with UB cigarettes will be followed.

5.2 Study Duration

Potential participants must be willing to participate in a study that involves four, 5-hour sessions over the course of 2-3 weeks.

We anticipate being able to enroll three participants per month and complete all study procedures, including data analysis within 18 months.

5.3 **Use of radiation***:* NA

5.4 **Use of Center for Magnetic Resonance Research***:* NA

6.0 Data and Specimen Banking

6.1 Storage and Access

Cigarette butts and biomarker specimens will be collected and stored at the study site (University of Minnesota - Tobacco Research Programs, 717 Delaware St. SE) until delivery to the Masonic Cancer Center's Dr. Irina Stepanov laboratory for storage and analysis. Samples that are not used for the primary analysis of study biomarkers will be banked for future use. The banked samples will be stored until analyses and destroyed if it is determined they are no longer needed. The samples, which may also include DNA or RNA, may be stored up to a maximum of 10 years from the study's end. A subject has the right to withdraw consent at any time by informing the Principal Investigator by following the instructions provided in the consent and HIPAA documents. If this occurs, any remaining identifiable research sample(s) will be destroyed.

6.2 Data

Data will be stored in a secure database (RedCap) and on University of Minnesota servers. Only study personnel directly involved with the study will have access to the linked records. The samples that will be transferred to the laboratory or stored for future analyses will be de-identified. We will not be transferring data that has any identifying information over the internet.

Biomarker samples (buccal cells) that are banked after the completion of the primary analyses will be stored at the Masonic Cancer Center Stepanov laboratory located at the Cancer and Cardiovascular Research Building for future use.

6.3 Release/Sharing

No identifying information will be shared with outside investigators. If used in any collaborative efforts beyond the scope of this study, any shared data will be de-identified. However, records for the study may be reviewed by departments at the University with appropriate regulatory oversight. The records may also be reviewed by a representative of the funding agency, National Institutes of Health, and the Food and Drug Administration.

7.0 Sharing of Results with Participants

7.1 Sharing of genetic testing

Information will not be shared with participants.

8.0 Study Population

8.1 Inclusion Criteria:

a) Male or female age 21 years or older;
b) Must smoke at least 5 cigarettes/day for at least 1 year (confirmed by CO >10 ppm or NicCheck test of 6 or greater);

c) Smoking cigarettes that have been evaluated to have medium levels of sugar content;
d) No quit attempts in the past month nor intentions to quit smoking in the next month;
e) Participants are in good physical health (no unstable medical conditions) as determined by the licensed medical professional;
f) Participants are in stable, good mental health (e.g. not currently, within the past 6 months, experiencing unstable or untreated psychiatric diagnosis) as determined by the licensed medical professional;
g) Stable vitals sign measurements (systolic BP ≤ 160 and >90 mmHg, diastolic BP ≤ 100 and >50 mmHg and heart rate ≤105 and > 45 bpm) as determined by the licensed medical professional
    a. Participants failing for vital signs will be allowed to re-screen once;
h) Participants must be able to read for comprehension or completion of study documents (confirmed during informed consent process);
i) Participants have provided written informed consent to participate in the study.

8.2 Exclusion Criteria:

a) Significant immune system disorders, respiratory diseases, kidney or liver diseases or any other medical disorders that may affect biomarker data as determined by the licensed medical professional;
b) Current or recent alcohol or drug abuse problems or use of substances of abuse (other than marijuana) in the past month;
c) Tobacco use other than cigarettes or marijuana for > 9 days per month
d) Current use (within past 2 weeks) of nicotine replacement or other tobacco cessation products;
e) Women who are pregnant or nursing or planning to become pregnant.
f) Frequent marijuana use. Quantified as >9 days of marijuana use in the last 30 days

8.3 Screening

Participants who agree to go through the pre- screening process will be assigned a screening number and taken through a screening questionnaire. Participants who meet the eligibility criteria described in section 8.1 and 8.2 will be asked to complete a more thorough screening visit, where the entire study will be explained in detail, informed consent will be obtained and the screening measures will be completed. The format for this visit will either be done in-person in the clinic or remotely via a secured-video conferencing link. In either scenario, participants will sign an e-consent.

9.0 Vulnerable Populations

9.1 Vulnerable Populations

No vulnerable populations will be used in the study.

10.0 Local Number of Participants

10.1 Local Number of Participants to be Consented

Up to 75 smokers will be consented in order to get 30 completers.

11.0 Local Recruitment Methods

11.1 Recruitment Process

We will recruit up to 75 adult smokers (30 completers) from the Minneapolis-St. Paul metro area who smoke at least 5 cigarettes per day. Smokers will be recruited through the University of Minnesota Tobacco Research Programs. A variety of media will be used that will foster the recruitment across a spectrum of age, education and socioeconomic status, and race/ethnicity.

11.2 Identification of Potential Participants

Participants will be recruited through various media (internet, television, newspaper, radio). Smokers will contact our clinic and be screened for eligibility over the telephone. During this screening, we will maximize retention of the participants between the screening and clinic visits by covering transportation costs and compensating them for their time. We will provide a respectful environment for the subject and train personnel on methods for minimizing subject dropouts.

11.3 Recruitment Materials

Participants will be recruited through printed flyers and advertisements through a variety of media outlets and the internet, including but not limited to, Facebook, newspapers, radio, and television ads.

11.4 Payment

Payment will be made using the Greenphire Clincard. Participants will be paid $25 for the screening visit and $25 for the baseline visit ($10 for transportation reimbursement, $15 for the study visit). Eligible participants will be paid $75 for each of the clinic visits ($10 for transportation reimbursement, $65 for the study visit x 4 visits = $300). Additionally, participants may earn up to an additional $5 each study visit based on the MCP questionnaire. At the end of the study, participants will be paid a $75 bonus for completing all sessions. The maximum total amount a participant will be paid is $445.

12.0 Withdrawal of Participants

12.1 Withdrawal Circumstances

A study participant may be discontinued from the study if investigators determine that this is the best decision in order to protect his/her safety. In the event that a participant either withdraws from the study or the investigators decide to discontinue a participant due to an adverse event (AE) or serious adverse event (SAE), the participant will have appropriate follow-up assessments and if necessary, referrals will be made for medical care. The participant experiencing an AE/SAE will be followed until the problem resolves, stabilizes, or is clearly unrelated to the study product. Any AE that remains open will be reviewed and closed at the last study visit.

12.2 Withdrawal Procedures

Subject will be informed about the withdrawal at the visit and data collection will stop.

12.3 Termination Procedures

No additional procedures will be conducted if participants are withdrawn.

13.0 Risks to Participants

13.1 Foreseeable Risks

The potential risks for participants recruited for this study are minimal. Potential risks for all participants include: emotional discomfort, breach of confidentiality, risks associated with smoking, risks to fetuses, and changes in blood pressure/heart rate.

Survey Questionnaires. The interviews will include questions about medical history, drug and alcohol use, and questionnaires about mood. Answering these personal questions could make the subject feel uncomfortable.

Risk of breach of confidentiality. There is always a small risk of breach of confidentiality. All subject samples and case report forms will be labeled with a unique numerical identifier in place of direct identifiers. The link between a participant and this unique identifier, and any other computer files containing direct identifiers will be kept in a password-protected file on a locked computer. Only the PI, study staff, and possibly approved regulatory officials (as required by the policies of the University of Minnesota and federal agencies such as the NIH, NCI, or FDA) will have access to direct identifiers. Case report forms with direct identifiers, demographic information and medical history will be kept separately and securely at all times.

Smoking Cigarettes. All cigarettes are detrimental to a person's health and can lead to severe or fatal medical problems including:

a. Cardiovascular Diseases: Coronary heart disease, heart attack, stroke, peripheral vascular disease, reduced blood circulation, abdominal aortic aneurysm
b. Respiratory Diseases: Emphysema, bronchitis, tuberculosis and chronic airway obstruction
c. Cancers: Lung, bladder, liver, colon, cervical, esophageal, kidney, larynx, mouth, pancreatic, throat, stomach cancers and acute myeloid leukemia

d. Diabetes
e. Immune function, rheumatoid arthritis
f. Other Health Risks Associated with Smoking: Including but not limited to infertility, ectopic pregnancy, lower bone density in postmenopausal women, hip fracture in women, male sexual dysfunction; age-related macular degeneration, blindness and cataracts

Study Cigarettes. The levels of sugar that will be added to study cigarettes will be no higher than those found in most popular cigarette brands. There is no additional risk to participants by using the study cigarettes.

At the end of the trial, participants will be strongly encouraged to stop use of all tobacco products and to set a quit date, and if requested, we will provide treatment resources and referral to different treatments including the state quit line.

Participants will be under medical supervision throughout their study participation and adverse symptoms will be recorded and monitored by the project PI, Dr. Hatsukami along with the study licensed medical professional.

13.2 Reproduction Risks

Pregnant women will not be recruited. If participants choose to be sexually active, they should use an appropriate "double barrier" method of birth control (such as female use of a diaphragm, intrauterine device (IUD), or contraceptive sponge, in addition to male use of a condom) or the female should be using prescribed "birth control" pills, injections, or implants. Female participants with child-bearing potential will be tested for pregnancy at the screening visit. If a participant becomes pregnant during the study, she will be withdrawn from the study. Approximately 30 days after being withdrawn or having a positive pregnancy test, the research staff will call the participant to confirm her due date. The licensed medical professional will follow-up with the participant after delivery to ask questions about the baby's health. A separate consent form will be signed in order to obtain data from pregnant participants.

13.3 Risks to Others

NA

14.0 Potential Benefits to Participants

14.1 Potential Benefits

Whereas no assurance can be made to an individual subject that he/she will personally benefit from such research, the experience should not impose any significant risk. Participants will have the opportunity to learn about factors that may be associated with tobacco use. Quitting tobacco will be strongly recommended to our participants and cessation materials will be provided if requested. Referrals to community resources can also be made.

15.0 Statistical Considerations

15.1 Data Analysis Plan

Trial design

The aim of this study is investigate the impact of sugar content in cigarette tobacco on cigarette abuse liability and appeal. The hypothesis is that the collected measures will indicate lower abuse liability for cigarettes with lowest sugar content.

This is a within-subject crossover study design with multiple periods and multiple treatments. The orders of the 3 sugar levels are counterbalanced using a Latin square, which will be created in advance by an independent statistician.

Trial endpoints

Outcome measures include subjective responses to cigarettes, behavioral measures, and mouth-level nicotine exposure.

Two *primary* outcome measures, which were used for power/sample size determination, include (1) the satisfaction of the Modified Cigarette Evaluation Questionnaire (mCEQ) and (2) the crossover point from the Multiple Choice Procedure task.

The other subjective and behavioral outcomes and mouth-level nicotine exposure will be *secondary*.

15.2 Power Analysis

A total of 30 completed participants will achieves >80% power, for each of the two primary outcomes (satisfaction and crossover point), to detect two sugar conditions (high vs. low)' difference of a moderate effect size (d = 0.6, the target scenario) at a 0.025 (= 0.05/2 primary outcomes) significance level, assuming a moderate correlation between sessions (r = 0.50) based on a T^2 test using PASS14 (NLSS, 2015). A total of up to 75 eligible smokers will be enrolled..

We note that because of the uncertainty of the effects of sugars and the range of effect sizes, we chose an effect size that is more conservative but near the range of the effect sizes (based on the endpoint of crossover point from the Multiple Choice Procedure task) used in most studies. The powers of the target scenario and other scenarios by changing the within-subject correlation and effect size, with the fixed sample size (n = 30) and type I error (α = 0.025), are presented in the table below. We note that the actual power for the factor of sugar level could be larger since 3 sugar levels will be studied.

Scenario	Power	Effect size (d)	Within-subject correlation (r)
Target scenario	0.81	0.6	0.5
	0.89	0.6	0.6
	0.64	0.5	0.5

Other scenarios	0.75	0.5	0.6
	0.92	0.7	0.5
	0.96	0.7	0.6

15.3 Statistical Analysis

General Approach

All statistical analyses will be performed using SAS or R. All statistical tests will be two-tailed. A Bonferonni adjustment will be used to account for 2 primary endpoints ($p < 0.025$ considered significant). Analyses of the secondary endpoints will not be adjusted ($p < 0.05$ considered significant). Proper transformation such as the logarithm transformation will be used to approximate normality for the outcome variables.

Describing the Study Population

Baseline characteristics of the participants will be summarized using mean and standard deviation (SD) for continuous variables and frequency and percentage for categorical variables.

Primary Analysis

The primary data analysis method will be linear mixed models including the two within-subject factors, sugar condition (2 dummy variables for the medium and high sugar levels) and time (2 dummies for the 3rd and 4th sessions), adjusted for the nicotine levels in spent filters of the first study cigarette used in each of the laboratory sessions (under the fixed puffing pattern). The potential carry-over effect will be tested by including the previous session's condition, i.e., 2 dummies for the previous session being medium and high sugar level (Diggle et al., 2002, p150-153). Note that the usual brand's measure (collected at the 1st session) and other participant-level factors are naturally adjusted across different sugar conditions because of the within-subject design, and hence are not included in the model. However, participant-level factors will be examined for any potential moderating effect (i.e., interaction) as an exploratory analysis.

Subgroup Analysis

Subgroup analyses will be performed for female and male smokers. The analyses will follow the same approach described for the overall group. Note that this study is not powered for detecting the potential interaction of gender and sugar level, however, we will report the size and significance of the interaction together with the subgroup analysis results to provide information for understanding of the role of gender.

Missing data

Every effort will be made to limit the amount of missing data in this trial, and study participants will be incentivized to attend study sessions. We anticipate a high retention rate (>80%) because of the short period of time of this laboratory study.

We will compare subjects who do and do not complete the study sessions in terms of their baseline characteristics. All observed data will be utilized in the analyses, with missing data being assumed to be missing at random, by using the mixed effects models.

15.4 Data Integrity

A variety of measures will be taken to ensure data accuracy and completeness. The regular research team meetings will include discussions of proper methods for data collection, transmission, and storage, limiting data collection to those in protocol required to answer a research question, de-identifying data, and encryption methods.

A comprehensive data dictionary will be created to specify definitions and value codes for all variables that will be entered into REDCap and other study databases. Electronic forms for the collection of subjective measures via REDCap will include programming features to ensure valid data (i.e., input masks, validation criteria, skipout logic) and will be stored on the University of Minnesota, HIPAA compliant, computing system. Double entry will be used for all other de-identified data entered into REDCap. Spent cigarette filters and biological specimens (oral cells) will be labeled with barcode labels that incorporate the participant ID. The secured biospecimen website will identify the location of each sample at the clinic (prior to submission to the laboratory) and in the Stepanov laboratory.

Oversight of the study cigarette distribution will be conducted by the Project Manager in collaboration with the co-Principal Investigators. The order of study cigarette use (sugar levels) will be generated by an independent statistician. The schedules and the link between the study cigarette code and order assignment will be maintained securely by the Project Manager. A Product Tracking database will be created to track study cigarette inventory and assignment of order to participants based on the randomization schedule.

Quality control procedures will be conducted for all data collected, including analysis of missing data, and logic checks for out of range and other anomalous values. Queries will be made regarding such data issues, with documentation of any changes made in the data.

16.0 Health Information and Privacy Compliance

16.1 Select which of the following is applicable to your research:

☐ My research does not require access to individual health information and therefore assert HIPAA does not apply.

☒ I am requesting that all research participants sign a HIPCO approved HIPAA Disclosure Authorization to participate in the research (either the standalone form or the combined consent and HIPAA Authorization).

☐ I am requesting the IRB to approve a Waiver or an alteration of research participant authorization to participate in the research.

☐ An external IRB (e.g. Advarra) is reviewing and we are requesting use of the authorization language embedded in the template consent form in lieu of the U of M stand-alone HIPAA Authorization. Note: External IRB must be serving as the privacy board for this option.

16.2 **Identify the source of Private Health Information you will be using for your research (Check all that apply)**

☐ I will use the Informatics Consulting Services (ICS) available through CTSI (also referred to as the University's Information Exchange (IE) or data shelter) to pull records for me

☒ I will collect information directly from research participants.

☐ I will use University services to access and retrieve records from the Bone Marrow Transplant (BMPT) database, also known as the HSCT (Hematopoietic Stem Cell Transplant) database.

☐ I will pull records directly from EPIC.

☐ I will retrieve record directly from axiUm / MiPACS

☐ I will receive data from the Center for Medicare/Medicaid Services

☐ I will receive a limited data set from another institution

☐ Other. Describe:

16.3 **Explain how you will ensure that only records of patients who have agreed to have their information used for research will be reviewed.**

Participants who are interested in the study will contact the Tobacco Research Programs. All PHI will be self-reported by the participant.

16.4 **Approximate number of records required for review**

NA

16.5 **Please describe how you will communicate with research participants during the course of this research. Check all applicable boxes**

☐ This research involves record review only. There will be no communication with research participants.

☐ Communication with research participants will take place in the course of treatment, through MyChart, or other similar forms of communication used with patients receiving treatment.

☒ Communication with research participants will take place outside of treatment settings. If this box is selected, please describe the type of communication and how it will be received by participants.

We will communicate with participants via phone, email and text messages. We will ask each participant for his or her preferred method of communication.

16.6 **Explain how the research team has legitimate access to patients/potential participants:**

All investigators and staff associated with this project have been trained, and new hires will be trained, on human research ethics and Good Clinical Practice in accordance with the requirements of the University of Minnesota.

16.7 **Location(s) of storage, sharing and analysis of research data, including any links to research data (check all that apply).**

☐ In the data shelter of the Information Exchange (IE)

☐ Store ☐ Analyze ☐ Share

☐ In the Bone Marrow Transplant (BMT) database, also known as the HSCT (Hematopoietic Stem Cell Transplant) Database

☐ Store ☐ Analyze ☐ Share

☒ In REDCap (recap.ahc.umn.edu)

☒ Store ☐ Analyze ☒ Share

☐ In Qualtrics (qualtrics.umn.edu)

☐ Store ☐ Analyze ☐ Share

☐ In OnCore (oncore.umn.edu)

☐ Store ☐ Analyze ☐ Share

☒ In the University's Box Secure Storage (box.umn.edu)

☒ Store ☒ Analyze ☒ Share

☒ In an AHC-IS supported server. Provide folder path, location of server and IT Support Contact:

\\tobacco.ahc.umn.edu\tobacco\TobaccoResearch\SugarsProject

☒ Store ☒ Analyze ☒ Share

☒ In an AHC-IS supported desktop or laptop.

Provide UMN device numbers of all devices:

Device #1: 20180114

☒ Store ☒ Analyze ☒ Share

☐ Other. Describe:

Indicate if data will be collected, downloaded, accessed, shared or stored using a server, desktop, laptop, external drive or mobile device (including a tablet computer such as an iPad or a smartform (iPhone or Android devices) that you have not already identified in the preceding questions

☐I will use a server not previously listed to collect/download research data

☐I will use a desktop or laptop not previously listed

☐I will use an external hard drive or USB drive ("flash" or "thumb" drives) not previously listed

☐I will use a mobile device such as an tablet or smartphone not previously listed

16.8 Consultants. Vendors. Third Parties

NA

16.9 Links to identifiable data

NA

16.10 Sharing of Data with Research Team Members

Data files will be stored in a UMN Box folder or on the Tobacco Research Programs shared server.

16.11 Storage and Disposal of Paper Documents

Paper files will be kept in subject binders in a locked file cabinet stored in a locked office. Original signed consent forms and other identifiable information will be kept separate from the research information. Paper files will be kept for the longest applicable standard as required by this study.

17.0 Confidentiality

17.1 Data Security

All investigators and staff associated with this project have been trained, and new hires will be trained, on human research ethics and Good Clinical Practice in accordance with the requirements of the University of Minnesota.

Only the immediate study team (Project Manager, Study Coordinator and Principal Investigators) will have access to individually identifiable private information about participants. Coded ID's will be used throughout the study by all the researchers involved. Because this study uses an investigational product and we are required to obtain Investigational Tobacco Product approval through the Food and Drug Administration, the records may potentially be monitored by this governmental agency. This information will be provided to the IRB and will be included in the human consent form. Original signed consent

forms and other identifiable information will be kept separate from the research information in a secure and locked space/database.

18.0 Provisions to Monitor the Data to Ensure the Safety of Participants

18.1 Data Integrity Monitoring

Oversight for quality control and adherence to protocol procedures will be conducted by the Project Manager in collaboration with the co-Principal Investigators. A start-up meeting with the whole research team will take place prior to participant enrollment. During this meeting, there will be training on the study protocol, standard operating procedures, equipment and data collection platforms. Independent monitoring of the study will be conducted by the University of Minnesota's Clinical and Translational Science Institute (CTSI) clinical trial monitoring service. The CTSI monitors will confirm that study activities are in compliance with the approved protocol and applicable regulatory authorities. The investigator will give the study monitors direct access to source documentation, study data, and relevant regulatory documentation.

Standard operating procedures will be developed for consistent implementation of the protocol. The Study Coordinator will be administering all measures during clinic visits and entering the information about each subject into a database. Each visit will have a checklist of all measures that need to be obtained and the order by which they will be administered. The Project Manager will be directly supervising the Study Coordinator and will periodically review protocol compliance and implementation, and adherence to good clinical practice procedures.

The Study Coordinator will go over the questionnaire instructions and will be available to the participant to answer any questions he/she may have. Questionnaires will be reviewed for completeness while the participant is present. Several biochemical measures (expired breath CO and urine pregnancy) will be analyzed immediately, while the participant is present. If necessary (e.g., if the sample volume is insufficient for analysis), the Study Coordinator can gather another sample immediately and re-analyze.

Once a participant has completed all study procedures and all open events have been closed, the PI will review the participant's binder and sign a form indicating study completion for that participant.

18.2 Data Safety Monitoring

This is a minimal risk, non-therapeutic study. While participating in the trial, AEs and concomitant medications will be assessed at every study visit and vital signs will be obtained. The Principal Investigator Dorothy Hatsukami and Co-Investigator Irina Stepanov will meet weekly with the study staff to review recruitment progress and any adverse events. Entrance criteria will be reviewed following screening. Study participants will be under medical supervision while in the study and our research

staff will make appropriate referrals to the physician should any adverse events occur.

AEs will typically be identified during the administration of the Health Changes Questionnaire. Other events may be identified from physiological study measures or by spontaneous reports during assessments.

If any questions arise regarding the health status of the participant before, during or after the laboratory session, either Drs. Hatsukami or Sharon Allen (medical director) will be available for consultation.

The study's Data and Safety Monitoring Plan will be in compliance with the University of Minnesota Masonic Cancer Center's Data & Safety Monitoring Plan (DSMP), which can be accessed at https://z.umn.edu/dsmp. For the purposes of data and safety monitoring, this study is classified as moderate risk. Therefore the following requirements will be fulfilled: The Masonic Cancer Center Data and Safety Monitoring Council (DSMC) will review the trial's progress twice yearly.

Assessment of Questionnaire Items

- Health Changes Questionnaire: If the participant answers 'YES' to Questions 1, 2, or 3, the interviewer will assess for an 'Adverse Event.'
    1) *Have you had any negative changes in your health since your last visit?*
    2) *Have you had any changes in medication since your last visit?*
    3) *Since your last visit, have you received any form of medical care?*

Adverse Events Communicated by Participants

The occurrence of AEs will be sought by non-directive questioning of the participant at each visit during the study. AEs also may be detected when the participant volunteers them during or between visits or through physical examination, laboratory test, or other assessments.

Review and Reporting of Adverse Events and Serious Adverse Events

Co-Principal Investigators with oversight from Sharon Allen, M.D. (Medical Monitor) will review all AEs and assess whether they are related to the study product.

An AE is defined as the appearance or worsening of any undesirable sign, symptom, or medical condition occurring after starting the study procedures even if the event is not considered to be related to the study product. Medical conditions/diseases present before starting the study are only considered adverse events if they worsen after starting the study product. Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant, or require therapy; there are no plans for active monitoring of laboratory tests as part of this project.

To the extent possible, each adverse event will be evaluated to determine:

1. the severity grade (mild, moderate, severe)
2. its relationship to the study product used (suspected/not suspected)
3. its duration (start and end dates or if continuing at final exam)

4. outcome (resolved/improved/unchanged/worsened; study product temporarily interrupted or permanently discontinued due to this adverse event; concomitant medication taken; non-drug therapy administered)
5. whether it constitutes a SAE

Information about all SAEs will be collected and recorded on the project's Serious Adverse Event Report Form. A SAE is defined an undesirable sign, symptom or medical condition which:

1. is fatal or life-threatening;
2. requires or prolongs hospitalization;
3. results in persistent or significant disability/incapacity;
4. constitutes a congenital anomaly or a birth defect;
5. is medically significant, in that it may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

Events not considered to be SAEs are hospitalizations that are:

1. elective or pre-planned, for a pre-existing condition that is unrelated to the products under study and did not worsen;
2. for general care, and/or overnight observation;
3. treatment on an emergency, outpatient basis for an event not fulfilling any of the definitions of serious given above and not resulting in hospital admission.

Safety evaluation will be performed on all accrued participants for whom study products were dispensed. The assessment of safety will be based on the frequency of AEs and severity grade of AEs. Other safety data (e.g. vital signs) will be considered as appropriate.

Any SAE occurring after the participant has signed the consent form and until the last encounter with the participant will be reported. All AEs will be summarized by presenting, for each treatment group, the number and percentage of participants who experienced any AE, the number reporting AEs in each body system and the number of AEs by type. Any other information collected (e.g., severity or relatedness to study product) will be listed as appropriate. A summary of clinically relevant toxic events, such as AEs leading to death or rated as SAEs, those with a suspected relationship to study product, or AEs requiring further medication or non-drug therapies will be provided. Reports will be reviewed regularly by the study investigators.

19.0 Provisions to Protect the Privacy Interests of Participants

19.1 Protecting Privacy

It will be made clear to participants that all information obtained during assessments is confidential and that no information will be shared with the participants' clinicians unless the participant requests this in writing.

While all the samples and information will be collected specifically to achieve the goals of this proposal, de-identified individual subject data and back-up samples may be made available to other researchers for research purposes after our study is complete. We will obtain permission from participants through the main consent process and form to allow de-

identified biosamples to be stored in a biorepository for future analyses of biomarkers or genotyping.

19.2 Access to Participants

There will be no access to medical records or any other sources of private information about the participating participants

20.0 Compensation for Research-Related Injury

20.1 Compensation for Research-Related Injury

The study poses minimal risk to participants. In the event of a research related injury, treatment will be provided. Such care will be billed to the participant or their insurance company in the ordinary manner.

20.2 Contract Language

NA

21.0 Consent Process

21.1 Consent Process (when consent will be obtained)

The consenting process will take place virtually via a secured video-conferencing meeting invitation or in-person at the Tobacco Research Programs (717 Delaware St SE). Potential participants will be told the nature of the research during pre-screening and then at the screening visit. They will be told they may discontinue participation at any time and will not be discriminated against if they choose to do so. Interested subjects will be provided considerable time to review the consent form, consider whether or not to participate, and have any questions answered by the coordinator. Participants will be required to demonstrate an understanding of the study purpose and procedures prior to signing the consent form. Assessment of the subject's understanding will be completed via questions by a slideshow presentation. The consent form must be signed before the research is started. Immediately after signing, the participant will receive an email with a signed copy of the consent form.

The electronic consent forms will be stored in a REDCap database with restricted access for essential study personnel only. The electronic informed consent (eIC) will be built using the 'UMN e-Consent HRP-592-TEMPLATE-Biomedical'. The template will be customized to match the written informed consent form exactly. The electronic signatures obtain in the outline above are intended to be the equivalent of handwritten signatures. Therefore, the electronic signatures will occur in accordance with the predicated rule (e.g. approved, reviewed and verified) as outlined in the Food and Drug Administration's CFR part 11.

21.2 Waiver or Alteration of Consent Process (when consent will not be obtained)

NA

21.3 Waiver of Written/Signed Documentation of Consent (when written/signed consent will not be obtained)

Participants will be screened over the phone or via a REDCap survey for initial eligibility using a recruitment script. All elements of consent are addressed in said script. Consent will be obtained prior to asking research related questions.

21.4 Non-English Speaking Participants

NA

21.5 Participants Who Are Not Yet Adults (infants, children, teenagers under 18 years of age)

NA

21.6 Cognitively Impaired Adults, or adults with fluctuating or diminished capacity to consent

NA

21.7 Adults Unable to Consent

NA

22.0 Setting

22.1 Research Sites

The study will be conducted at the University of Minnesota, Twin Cities

- Subject recruitment and sample collection will take place at Tobacco Research Programs (717 Delaware St. SE, Minneapolis, MN 55414).
- Biochemical analysis will be carried out in the Masonic Cancer Center (2231 6th St. SE, Minneapolis, MN 55455).

22.2 International Research

NA

23.0 Multi-Site Research

NA

23.1 Study-Wide Number of Participants

NA

23.2 Study-Wide Recruitment Methods

NA

23.3 Study-Wide Recruitment Materials

NA

23.4 Communication Among Sites

23.5 Communication to Sites

NA

24.0 Coordinating Center Research

NA

24.1 Role:
24.2 Responsibilities:
24.3 Oversight:
24.4 Collection and Management of Data:

25.0 Resources Available

25.1 Resources Available

The study will be conducted at the University of Minnesota's Tobacco Research Programs housed at the Delaware Clinical Research Unit at 717 Delaware St. SE Minneapolis, MN. Dr. Dorothy Hatsukami serves as the Director for this Program. We have a Research Project Manager who oversees all research and is responsible for logistics of implementing the protocols and standard operating procedures. She is also responsible for the quality control of the projects by ensuring that all studies follow ethical scientific standards and that procedures meet GCP standards, that all regulatory forms are completed including Institutional Review Board applications, and that the DSMB process is in place. She has been working in this capacity for over 10 years. We also have an Administrator who ensures the smooth operation of the daily activities of the Program. In addition, the Program has a registered nurse practitioner and many research project coordinators. The shared space at the Delaware Clinical Research Units includes a shared waiting room with a receptionist, 7 physical exam rooms (two dedicated to the Tobacco Research Programs), 1 phlebotomy room, 5 interview rooms, 2 day hospital rooms, an infusion room, 1 smoking laboratory with one way observation room, laboratory space for processing blood, urine processing laboratory, a locked medication supply room, locked protocol room for subject files, cubicles for data entry, management and analyses, locked supply storage and access to three conference rooms. Two restrooms are in the clinical space for urine collections. We have dedicated space for our biorepository with key card access containing ten -20 freezers. We also have access to all of the resources of the University of Minnesota for our use, as needed.

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ANCILLARY REVIEWS

DO NOT DELETE. Submit the completed checklist below with your protocol.

Which ancillary reviews do I need and when do I need them? Refer to HRP-309 for more information about these ancillary reviews.			
Select yes or no	**Does your study…**	*If yes…*	***Impact on IRB Review***
☐ **Yes** ☒ **No**	Include Gillette resources, staff or locations	*Gillette Scientific review and Gillette Research Administration approval is required. Contact: research@gillettechildrens.com*	**Required prior to IRB submission**
☐ **Yes** ☒ **No**	Involve Epic, or Fairview patients, staff, locations, or resources?	*The Fairview ancillary review will be assigned to your study by IRB staff Contact:* ancillaryreview@Fairview.org	**Approval must be received prior to IRB committee/ designated review.** **Consider seeking approval prior to IRB submission.**
☒ **Yes** ☐ **No**	Include evaluation of drugs, devices, biologics, tobacco, or dietary supplements or data subject to FDA inspection?	*The regulatory ancillary review will be assigned to your study by IRB staff Contact: medreg@umn.edu* *See: https://policy.umn.edu/research/indide*	
☐ **Yes** ☒ **No**	Require Scientific Review? Not sure? See guidance in the Investigator Manual (HRP-103).	*Documentation of scientific merit must be provided. Contact: hrpp@umn.edu*	
☒ **Yes** ☐ **No**	Relate to cancer patients, cancer treatments, cancer screening/prevention, or tobacco?	*Complete the CPRC application process. Contact: ccprc@umn.edu*	
☐ **Yes** ☒ **No**	Include the use of radiation? (x-ray imaging, radiopharmaceuticals, external beam or brachytherapy)	*Complete the AURPC Human Use Application and follow instructions on the form for submission to the AURPC committee. Contact: barmstro@umn.edu*	**Approval from these committees must be received prior to IRB approval;** **These groups**
☐ **Yes** ☒ **No**	Use the Center for Magnetic Resonance Research (CMRR) or MR at Masonic Institute for the Developing Brain (MIDB) as a study location?	*Complete the CMRR pre-IRB ancillary review Contact: ande2445@umn.edu*	

☐ **Yes** ☒ **No**	Include the use of recombinant or synthetic nucleic acids, toxins, or infectious agents?	*Complete the IBC application via eprotocol.umn.edu*	**each have their own application process.**
☐ **Yes** ☒ **No**	Include the use of human fetal tissue, human embryos, or embryonic stem cells?	*Contact OBAO for submission instructions and guidance*	
☐ **Yes** ☒ **No**	Include PHI or are you requesting a HIPAA waiver?	*If yes, HIPCO will conduct a review of this protocol.* *Contact: privacy@umn.edu*	
☐ **Yes** ☒ **No**	Include the use of a controlled substance?	*If yes, University Health and Safety Compliance for controlled substances will review the protocol.* *Contact:* cshelp@umn.edu	**Approval must be received prior to IRB approval.** **These groups do not have a separate application process but additional information from the study team may be required.**
☒ **Yes** ☐ **No**	Plan to use CTSI Monitoring services, and/or have an IND, IDE, or designated NSR-IDE by the UMN IRB?	*The CTSI monitoring ancillary review will be assigned to your study by IRB staff.* *Please note eligibility criteria here.* *Contact:* fencl003@umn.edu	
☐ **Yes** ☒ **No**	Use data from CTSI Best Practices Integrated Informatics Core (BPIC) Formerly the AHC Information Exchange (IE)?	*The Information Exchange ancillary review will be assigned to your study by IRB staff* *Contact:* bpic@umn.edu	
☐ **Yes** ☒ **No**	Use the Biorepository and Laboratory Services to collect tissue for research?	*The BLS ancillary review will be assigned to your study by IRB staff.* *Contact: Jenny Pham* *Pham0435@umn.edu*	
☐ **Yes** ☒ **No**	Have a PI or study team member with a conflict of interest?	*The CoI ancillary review will be assigned to your study by IRB staff* *Contact: becca002@umn.edu*	
☒ **Yes** ☐ **No**	Need to be registered on clinicaltrials.gov?	*If you select "No" in ETHOS, the clinicaltrials.gov ancillary review will be assigned to your study by IRB staff* *Contact:* fencl003@umn.edu	
☒ **Yes** ☐ **No**	Require registration in OnCore?	*If you select "No" or "I Don't Know" in ETHOS, the OnCore ancillary review will be assigned to your study by IRB staff* *Contact: oncore@umn.edu*	**Does not affect IRB approval.**
