HRP-591 - Protocol for Human Subject Research

Protocol Title:

Provide the full title of the study as listed in item 1 on the "Basic Information" page in CATS IRB (http://irb.psu.edu).

Peanut consumption, blood sugar control, and gut health

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Version Date:

Provide the date of this submission. This date must be updated each time the submission is provided to the IRB office with revisions.

September 4, 2019

Clinicaltrials.gov Registration #:

Provide the registration number for this study, if applicable.

NCT03654651

Important Instructions for Using This Protocol Template:

1. Add this completed protocol template to your study in CATS IRB (http://irb.psu.edu) on the "Basic Information" page, item 7.
2. This template is provided to help investigators prepare a protocol that includes the necessary information needed by the IRB to determine whether a study meets all applicable criteria for approval.
3. **Type your protocol responses below the gray instructional boxes of guidance language. If the section or item is not applicable, indicate not applicable.**
4. **For research being conducted at Penn State Hershey or by Penn State Hershey researchers only, delete the instructional boxes from the final version of the protocol prior to upload to CATS IRB (http://irb.psu.edu). For all other research, do not delete the instructional boxes from the final version of the protocol.**
5. When making revisions to this protocol as requested by the IRB, please follow the instructions outlined in the Study Submission Guide available in the Help Center in CATS IRB (http://irb.psu.edu) for using track changes.

If you need help...	
University Park and other campuses: Office for Research Protections Human Research Protection Program The 330 Building, Suite 205	**College of Medicine and Hershey Medical Center:** Human Subjects Protection Office 90 Hope Drive, Mail Code A115, P.O. Box 855

University Park, PA 16802-7014 Phone: 814-865-1775 Fax: 814-863-8699 Email: irb-orp@psu.edu	Hershey, PA 17033 (Physical Office Location: Academic Support Building Room 1140) Phone: 717-531-5687 Fax number: 717-531-3937 Email: irb-hspo@psu.edu

Table of Contents

1.0 Objectives

1.1 Study Objectives

Describe the purpose, specific aims or objectives. State the hypotheses to be tested.

The purpose of the study is to evaluate the effects of nighttime peanut consumption (i.e., after dinner and before sleep) on fasting blood glucose levels, longer-term blood glucose control, and risk factors for cardiovascular disease. Furthermore, this study will investigate the relationship between the microbiota, shifts in the microbiota with peanut consumption and the effect on blood glucose regulation. There is some emerging evidence that the microbiome predicts glycemic response and this study would provide the first robust test of the role of the microbiome in blood glucose regulation in response to peanut consumption.

The aims of the study are as follows:
- To determine the effect of consuming one ounce of peanuts as an evening snack (after dinner and before sleep) on glycemic control and risk factors for cardiovascular disease, compared with an isocaloric high carbohydrate snack, in people with impaired fasting glucose.
- To assess changes in the profile of the gut bacterial community in response to the peanut treatment, compared with an isocaloric high carbohydrate snack, in people with impaired fasting glucose.
- To investigate the relationship between markers of glycemic control, after each treatment, and shifts in the microbiota to elucidate the role of the microbiome in glucose regulation.

Hypothesis
- consuming peanuts as an evening snack will reduce fasting glucose levels compared to an isocaloric high carbohydrate control snack.
- Improvements in fasting glucose levels with peanut consumption will be correlated with favorable shifts in the microbiota i.e. peanut consumption will result in enrichment of bacteria known to be biomarkers of a healthy gut and these shifts will be associated with the magnitude of blood glucose lowering observed.

1.2 Primary Study Endpoints

State the primary endpoints to be measured in the study. Clinical trials typically have a primary objective or endpoint. Additional objectives and endpoints are secondary. The endpoints (or outcomes), determined for each study subject, are the quantitative measurements required by the objectives. Measuring the selected endpoints is the goal of a trial (examples: response rate and survival).

Fasting plasma glucose

1.3 Secondary Study Endpoints

State the secondary endpoints to be measured in the study.

- Fructosamine
- Fasting insulin
- Microbiome
- Peripheral and central blood pressure
- Augmentation index
- Pulse wave velocity
- Lipids/lipoproteins
- Weight
- Dietary intake (calorie, macronutrient and overall diet quality).

2.0 Background

2.1 Scientific Background and Gaps

Describe the scientific background and gaps in current knowledge.

Approximately 34% of adults in the U.S. have pre-diabetes[1], defined as impaired fasting glucose or impaired glucose tolerance, placing them at substantially higher risk of developing type 2 diabetes[2]. Seventy-five percent of middle-aged people with pre-diabetes will develop type 2 diabetes in their lifetime[3]. In addition, individuals with pre-diabetes also present with a greater number of cardiovascular risk factors[4] and have a 10-20% higher risk of cardiovascular disease[5]. Therefore, it is a **public health priority** to identify strategies to reduce fasting blood glucose in individuals with pre-diabetes to delay the onset of type 2 diabetes.

A number of observational studies show nut consumption reduces diabetes risk[6-8]. A pooled analysis of five prospective cohort studies and one randomized controlled trial showed a 13% reduction in type 2 diabetes risk with consumption of 4 servings (28.4 g/serving) of nuts per week[6]. A more recent systematic review and meta-analysis of four studies showed that per 28 g/day of peanuts and tree nuts, risk of diabetes mortality was reduced by 39%[7]. There is convincing evidence from observational research to show that nuts, including peanuts reduce diabetes risk, and this is likely mediated by improvements in blood glucose control.

The effect of consuming peanuts as an evening snack on fasting glucose levels has not been tested. This is despite the clinical observations that fasting blood glucose is lower when nuts or nut butters are consumed in the evening. Adding support to these clinical observations is a study showing that a pre-bedtime snack of uncooked corn starch (Extend bar), a slow digesting, complex carbohydrate prevented overnight blood glucose excursions and reduced fasting blood glucose levels in adults with type 2 diabetes[9].

These observations may be explained in part by a blunting of the Dawn Phenomenon. The Dawn Phenomenon is characterized by a rise in early morning fasting blood glucose[10]. A present it is thought that the Dawn Phenomenon is caused by excessive glucose production by the liver “at dawn”, in the absence of insulin, and thus elevations in fasting blood glucose are observed[11]. Identifying successful strategies to counteract this physiological effect is of importance because a rise in fasting blood glucose levels of more than 50 mg/dL can result in daylong hyperglycemia[12]. Furthermore, the Dawn Phenomenon is not effectively treated by the current oral hypoglycemic agents and therefore an opportunity exists to identify an effective strategy to blunt the Dawn Phenomenon, a substantial cause of poor glycemic control[13], and improve overall glycemic control.

Emerging evidence suggests that the microbiome may determine glycemic response. Large individual variation has been observed in glycemic response to foods differing in glycemic index[14], and this has largely been poorly understood. However, recently, a one-week randomized controlled trial of two different bread treatments showed that the glycemic response to the bread type could be predicted based on the microbiome[15]. This paper, published in Cell Metabolism (impact factor 18.16), provides some of the first evidence that the microbiome may mediate glycemic response. Although this study was only one week long so changes in the microbiome could not be detected. Therefore, we propose to conduct a 6 week study to allow investigation of: 1) the effect of the microbiome on glycemic response to peanuts vs. the control snack; and 2) how changes in the microbiome in response to peanut consumption correlate with changes in glucose regulation.

Recent data suggests that tree nut consumption for between three and six weeks changes the microbiome[16-19]; no studies have assessed the effect of peanuts on the microbiome. In many of these studies there were changes in the relative abundance of microbiota known to be associated with beneficial health effects.

2.2 Previous Data

Describe any relevant preliminary data.

Previous meal studies from our lab and others have demonstrated that consumption of peanuts with a meal reduces post-meal blood glucose levels. In a study led by Dr. Kris-Etherton, blood glucose levels were lower 4 hours after consumption of a high-saturated fat beverage with 3 oz. of peanuts, compared to a high-saturated

fat beverage with 42 g of an oil blend reflecting the fatty acid composition of the peanut beverage[20]. In a similar study, it was shown that consuming peanuts with a high glycemic index (GI) meal improved 60-minute blood glucose response by 60% compared to the control in healthy subjects[21]. There is also evidence showing that the addition of peanuts to a meal improves blood glucose response to the subsequent meal. Reis *et al.*[22] reported that adding 42.5 g (1.5oz) of peanuts or peanut butter to a breakfast meal improved second meal blood glucose levels in obese women. These studies suggest that peanuts or peanut butter have a favorable effect on postprandial glucose levels.

There is also a growing body of evidence showing that nut consumption improves longer term glycemic control and risk factors for cardiovascular disease[23]. A meta-analysis of 12 randomized controlled trials, showed that tree nut consumption reduced fasting blood glucose in individuals with type 2 diabetes by 0.15 mmol/L after approximately 8 weeks[24]. We recently updated this meta-analysis and included all studies examining the effect of tree nuts and peanuts in adults *(unpublished).* Overall, there were improvements in insulin resistance and fasting insulin with nut consumption. A trend towards improvements in fasting blood glucose with nut consumption was also observed. In this review, five randomized controlled trials were identified that assessed the effect of peanuts on blood glucose levels, and these studies were heterogeneous in design, however in all of the studies the timing of peanut consumption was not controlled. We hypothesize that nighttime consumption of peanuts will result in improvements in fasting glucose levels based on known physiology and research demonstrating the glycemic benefit of evening consumption of healthful snacks.

2.3 Study Rationale

Provide the scientific rationale for the research.

There has been limited investigation of the influence of peanuts on fasting blood glucose, however based on the effects of peanuts and peanut butter on other markers of diabetes control including post-prandial blood glucose and circulating insulin levels, there is biologic plausibility for this hypothesis. Many of the studies that have been conducted have included healthy populations[25-27], and these findings cannot be generalized to people with pre-diabetes due to the poor glycemic regulation present in pre-diabetes. In addition, not all of the studies done to date have included nutrition counseling on timing and serving sizes of nuts added to the diet[26, 28]. We hypothesize that consumption of peanuts in the evening (after dinner and before sleep) will have a greater impact on fasting glucose than consumption at other times of the day. This is because peanuts and peanut butter are rich in MUFA, which delay gastric emptying and promote a slow and sustained release of carbohydrate that may act to stabilize overnight blood glucose levels and reduce the spike in glucose levels seen in the early morning, which makes subsequent glucose control throughout the day challenging.

The proposed project will generate **high quality robust data** in a cohort with pre-diabetes for: 1) the effect of consuming one ounce of peanuts as an evening snack (after dinner and before sleep) on glycemic control and risk factors for cardiovascular disease, compared with an isocaloric high carbohydrate snack; 2) changes that occur in the profile of the gut bacterial community in response to peanut consumption compared with an isocaloric high carbohydrate snack; 3) the relationship between markers of glycemic control and shifts in the microbiota in response to peanut consumption to elucidate the role of the microbiome in glucose regulation.

3.0 Inclusion and Exclusion Criteria

Create a numbered list below in sections 3.1 and 3.2 of criteria subjects must meet to be eligible for study enrollment (e.g., age, gender, diagnosis, etc.). Indicate specifically whether you will include any of the following vulnerable populations: (You may not include members of these populations as subjects in your research unless you indicate this in your inclusion criteria.) Review the corresponding checklists to ensure that you have provided the necessary information.

- **Adults unable to consent**

- Review "CHECKLIST: Cognitively Impaired Adults (HRP-417)" to ensure that you have provided sufficient information. HRP-417 can be accessed by clicking the Library link in CATS IRB (http://irb.psu.edu).

- **Individuals who are not yet adults (infants, children, teenagers)**
  - If the research involves persons who have not attained the legal age for consent to treatments or procedures involved in the research ("children"), review the "CHECKLIST: Children (HRP-416)" to ensure that you have provided sufficient information. HRP-416 can be accessed by clicking the Library link in CATS IRB (http://irb.psu.edu).
- **Pregnant women**
  - Review "CHECKLIST: Pregnant Women (HRP-412)" to ensure that you have provided sufficient information. HRP-412 can be accessed by clicking the Library link in CATS IRB (http://irb.psu.edu).
- **Prisoners**
  - Review "CHECKLIST: Prisoners (HRP-415)" to ensure that you have provided sufficient information. HRP-415 can be accessed by clicking the Library link in CATS IRB (http://irb.psu.edu).
- **Neonates of uncertain viability or non-viable neonates**
  - Review "CHECKLIST: Neonates (HRP-413)" or "CHECKLIST: Neonates of Uncertain Viability (HRP-414)" to ensure that you have provide sufficient information. HRP-413 and HRP-414 can be accessed by clicking the Library link in CATS IRB (http://irb.psu.edu).

3.1 Inclusion Criteria

List the criteria that define who will be included in your study.

Participants will be non-smoking males and females aged 18 to 75 years with impaired fasting glucose at screening (≥ 100 mg/dL). Participants will have a BMI ≥20 and ≤40 kg/m^2.

3.2 Exclusion Criteria

List the criteria that define who will be excluded in your study.

We will not recruit participants who have chronic disease risk factors that are diagnostic of diabetes (fasting glucose > 126 mg/dL) or hypertension (SBP >160 mm Hg or DBP > 100 mm Hg). In addition, they will not be taking anti-hypertensive, lipid lowering or glucose lowering drugs. Individuals with established CVD, stroke, diabetes, liver, kidney, autoimmune diseases or inflammatory conditions such as gastrointestinal disorders or rheumatoid arthritis will not be eligible. Other exclusion criteria will include: use of supplements (psyllium, fish oil, soy lecithin, and phytoestrogens) and botanicals and not willing to cease for the duration of the study; women who are pregnant, lactating, planning to become pregnant or have given birth in the past year; weight loss of ≥10% of body weight within the 6 months prior to enrolling in the study; or smoking or use of any tobacco products in past 6 months. Participants with an allergy/intolerance/sensitivity to test foods will be excluded (i.e. peanuts, gluten, grain products, cheese). Individuals consuming >14 alcoholic drinks/week or not willing to avoid alcohol consumption for 48 hour prior to test visit will be ineligible for the study.

3.3 Early Withdrawal of Subjects

3.3.1 Criteria for removal from study

Insert subject withdrawal criteria (e.g., safety reasons, failure of subject to adhere to protocol requirements, subject consent withdrawal, disease progression, etc.).

Failure to comply with study procedures.
Participant withdraws consent.

3.3.2 Follow-up for withdrawn subjects

Describe when and how to withdraw subjects from the study; the type and timing of the data to be collected for withdrawal of subjects; whether and how subjects are to be replaced; the follow-up for subjects withdrawn from investigational treatment.

No safety concerns; no reason for follow-up. If consent is withdrawn no data from the participant will be used. Otherwise, if consent is not withdrawn, data from individuals who withdraw from the study may be used in an intent-to-treat analysis but another individual will be enrolled to ensure that an adequate sample size (with complete data) is reached.

4.0 Recruitment Methods

4.1 Identification of subjects

Describe the methods that will be used to identify potential subjects or the source of the subjects. If not recruiting subjects directly (e.g., database query for eligible records or samples) state what will be queried, how and by whom.
StudyFinder: If you intend to use StudyFinder (http://studyfinder.psu.edu) for recruitment purposes, please indicate this in section 4.1 along with any other methods for identifying subjects. Note that information provided in this protocol should be consistent with information provided on the StudyFinder page in your CATS IRB study.

For Penn State Hershey submissions using Enterprise Information Management (EIM) for recruitment, attach your EIM Design Specification form on the Basic Information page in CATS IRB (http://irb.psu.edu). See HRP-103 Investigator Manual, "What is appropriate for study recruitment?" for additional information.

Flyer/posters will be placed in campus buildings and facilities as well as the surrounding area (gyms, churches, supermarkets, coffee shops etc.) to identify potential subjects residing in and around the State College. Ads will also be placed in the local papers, magazines (e.g Centre Daily Times) and coupon mailers (e.g. Valpak), which are distributed to residential homes. In addition, radio ads will be run. Websites (e.g. http://clinicaltrials.gov/, Facebook, Craig's List), and PSU listservs will be used to advertise the study. We also will contact individuals who have participated in previous studies and indicated to our research group that they are interested in participating in future studies. A letter to local businesses or organization may be utilized requesting they share study details with their members/employees if permitted.

4.2 Recruitment process

Describe how, where and when potential subjects will be recruited (e.g., approaching or providing information to potential subjects for participation in this research study).

Public advertisements (flyers/posters/ newspaper ads/circulars/ websites and social media/ radio) in the local community (State College/ University Park area) will be used to recruit people. These ads will be run periodically depending on recruitment. When an individual responds to an ad, study staff will contact the individual using the contact details provided.

A letter to local businesses or organization may be utilized requesting they share study details with their members/employees if permitted.

All of these methods of recruitment will be used until the target sample size is reached.

4.3 Recruitment materials

List the materials that will be used to recruit subjects. Add recruitment documents to your study in CATS IRB (http://irb.psu.edu) on the "Consent Forms and Recruitment Materials" page. For advertisements, upload the final copy of printed advertisements. When advertisements are taped for broadcast, attach the final audio/video tape. You may submit the wording of the advertisement prior to taping to preclude re-taping because of inappropriate wording, provided the IRB reviews the final audio/video tape.

StudyFinder: If you intend to use StudyFinder (http://studyfinder.psu.edu) for recruitment purposes, you do not need to upload a separate recruitment document for information placed on the StudyFinder site to your study in CATS IRB. Necessary information will be captured on the StudyFinder page in your CATS IRB study.

Flyer and print ad (used for Newspaper and Magazine advertisement, circular ads, websites)
PSU Newswire, email, or list-serve advertisement
Letter: a letter to local businesses or organizations may be utilized requesting they share study details with their members/employees.
Radio ad

4.4 Eligibility/screening of subjects

If potential subjects will be asked eligibility questions before obtaining informed consent, describe the process. Add the script documents and a list of the eligibility questions that will be used to your study in CATS IRB (http://irb.psu.edu) on the "Consent Forms and Recruitment Materials" page.

StudyFinder: If you intend to use StudyFinder (http://studyfinder.psu.edu) for recruitment purposes, any scripts (phone, email, or other) used when contacting StudyFinder participants as well as any eligibility screening questions must be added to your study in CATS IRB (http://irb.psu.edu) on the "Consent Forms and Recruitment Materials" page.

Potential subjects who have responded to advertisements will be asked eligibility questions via a telephone screening before informed consent is obtained (refer to telephone screening form for complete list of screening questions). If you do not qualify for the study, the general reason why you did not qualify for the study will be recorded under an assigned screening study ID#. Documents containing information gathered during the telephone screening will be stored in a locked cabinet in 317 Chandlee lab or in a password protected file on a secure network. If you do qualify for the study, information gathered during the telephone screening such as names, addresses, telephone numbers, email addresses, date of birth, and visit dates will be linked to data via a code break list. Once enrolled in the study, all data collection will be performed under an assigned study ID# that is known only to the principal investigators, study coordinators and CRC staff (for purposes of blood collection and safety). These are the only persons able to connect the participant's identifiable information.

5.0 Consent Process and Documentation

Refer to "SOP: Informed Consent Process for Research (HRP-090)", for information about the process of obtaining informed consent from subjects. HRP-090 can be accessed by clicking the Library link in CATS IRB (http://irb.psu.edu).

5.1 Consent Process

5.1.1 Obtaining Informed Consent

5.1.1.1 Timing and Location of Consent

Describe where and when the consent process will take place.

After a brief telephone conversation explaining the study and answering some preliminary screening questions, a screening appointment will be scheduled at the Clinical Research Center (CRC). At this appointment, before any procedures take place, potential participants will be given the informed consent document. Following standard protocol procedure, a trained staff person will review the information in detail, make sure the individual understands the study and answers any questions they may have. If the participant is still interested in continuing with the screening process, both the participant and the staff member will sign and date the document. A copy of the sign consent document will be provided to the participant.

5.1.1.2 Coercion or Undue Influence during Consent

Describe the steps that will be taken to minimize the possibility of coercion or undue influence in the consent process.

Study staff, coordinators, and investigators who are fully trained in the recruiting process will respond to potential participants during recruitment so as to avoid any coercion or undue influence.

5.1.2 Waiver or alteration of the informed consent requirement

If you are requesting a waiver or alteration of consent (consent will not be obtained, required information will not be disclosed, or the research involves deception), describe the rationale for the request in this section. If the alteration is because of deception or incomplete disclosure, explain whether and how subjects will be debriefed. Add any debriefing materials or document(s) to your study in CATS IRB (http://irb.psu.edu) on the "Supporting Documents" page. NOTE: Review the "CHECKLIST: Waiver or Alteration of Consent Process (HRP-410)" to ensure you have provided sufficient information for the IRB to make these determinations. HRP-410 can be accessed by clicking the Library link in CATS IRB (http://irb.psu.edu).

Not applicable

5.2 Consent Documentation

5.2.1 Written Documentation of Consent

Refer to "SOP: Written Documentation of Consent (HRP-091)" for information about the process to document the informed consent process in writing. HRP-091 can be accessed by clicking the Library link in CATS IRB (http://irb.psu.edu).

If you will document consent in writing, describe how consent of the subject will be documented in writing. Add the consent document(s) to your study in CATS IRB (http://irb.psu.edu) on the "Consent Forms and Recruitment Materials" page. Links to Penn State's consent templates are available in the same location where they are uploaded and their use is required.

At their scheduled screening clinic appointment, before any procedures take place, potential participants will be given the informed consent document. Trained research personnel will make sure the individual understands the study expectations and will answer any questions they

may have. If the participant still is interested in continuing with the screening process, both the participant and the staff member will sign and date the document. A copy of the consent document will be provided to the participant. Signed original copies will be kept on file by the PI.

5.2.2 Waiver of Documentation of Consent (Implied consent, Verbal consent, etc.)

If you will obtain consent (verbal or implied), but not document consent in writing, describe how consent will be obtained. Add the consent script(s) and/or information sheet(s) to your study in CATS IRB (http://irb.psu.edu) on the "Consent Forms and Recruitment Materials" page. Links to Penn State's consent templates are available in the same location where they are uploaded and their use is required. Review "CHECKLIST: Waiver of Written Documentation of Consent (HRP-411)" to ensure that you have provided sufficient information. HRP-411 can be accessed by clicking the Library link in CATS IRB (http://irb.psu.edu).

If your research presents no more than minimal risk of harm to subjects and involves no procedures for which written documentation of consent is normally required outside of the research context, the IRB will generally waive the requirement to obtain written documentation of consent.

Verbal consent to participant in the telephone screening will be obtained. The telephone screening involves minimal risk and involves no procedures for which written documentation of consent is normally required outside of the research context. The questions asked are only those needed to ascertain whether a person may be eligible for the study and include contact details, and yes or no responses to a number of questions about dietary habits, food allergies, medical history and lifestyle. Thus, the only risk is that of minor discomfort when being asked questions related to lifestyle and personal medical history.

5.3 Consent – Other Considerations

5.3.1 Non-English Speaking Subjects

Indicate what language(s) other than English are understood by prospective subjects or representatives.

If subjects who do not speak English will be enrolled, describe the process to ensure that the oral and written information provided to those subjects will be in that language. Indicate the language that will be used by those obtaining consent.

Indicate whether the consent process will be documented in writing with the long form of the consent documentation or with the short form of the consent documentation. Review the "SOP: Written Documentation of Consent (HRP-091)" and the "Investigator Manual (HRP-103)" to ensure that you have provided sufficient information. HRP-091 and HRP-103 can be accessed by clicking the Library link in CATS IRB (http://irb.psu.edu).

Not applicable

5.3.2 Cognitively Impaired Adults

Refer to "CHECKLIST: Cognitively Impaired Adults (HRP-417)" for information about research involving cognitively impaired adults as subjects. HRP-417 can be accessed by clicking the Library link in CATS IRB (http://irb.psu.edu).

5.3.2.1 Capability of Providing Consent

Describe the process to determine whether an individual is capable of consent.

Not applicable.

5.3.2.2 Adults Unable To Consent

Describe whether and how informed consent will be obtained from the legally authorized representative. Describe who will be allowed to provide informed consent. Describe the process used to determine these individual's authority to consent to research.

For research conducted in the state, review "SOP: Legally Authorized Representatives, Children and Guardians (HRP-013)" to be aware of which individuals in the state meet the definition of "legally authorized representative". HRP-013 can be accessed by clicking the Library link in CATS IRB (http://irb.psu.edu).

For research conducted outside of the state, provide information that describes which individuals are authorized under applicable law to consent on behalf of a prospective subject to their participation in the procedure(s) involved in this research. One method of obtaining this information is to have a legal counsel or authority review your protocol along with the definition of "children" in "SOP: Legally Authorized Representatives, Children, and Guardians (HRP-013)." HRP-013 can be accessed by clicking the Library link in CATS IRB (http://irb.psu.edu).

Not applicable.

5.3.2.3 Assent of Adults Unable to Consent

Describe the process for assent of the subjects. Indicate whether assent will be required of all, some or none of the subjects. If some, indicate which subjects will be required to assent and which will not.

If assent will not be obtained from some or all subjects, provide an explanation of why not.

Describe whether assent of the subjects will be documented and the process to document assent. The IRB allows the person obtaining assent to document assent on the consent document and does not routinely require assent documents and does not routinely require subjects to sign assent documents.

Not applicable.

5.3.3 Subjects who are not yet adults (infants, children, teenagers)

5.3.3.1 Parental Permission

Describe whether and how parental permission will be obtained. If permission will be obtained from individuals other than parents, describe who will be allowed to provide permission. Describe the process used to determine these individual's authority to consent to each child's general medical care.

For research conducted in the state, review "SOP: Legally Authorized Representatives, Children and Guardians (HRP-013)" to be aware of which individuals in the state meet the definition of "children". HRP-013 can be accessed by clicking the Library link in CATS IRB (http://irb.psu.edu).

For research conducted outside of the state, provide information that describes which persons have not attained the legal age for consent to treatments or procedures involved in the research, under the applicable law of the jurisdiction in which research will be conducted. One method of obtaining this information is to have a legal counsel or authority review your protocol along with the definition of "children" in "SOP: Legally Authorized Representatives, Children, and Guardians (HRP-013)." HRP-013 can be accessed by clicking the Library link in CATS IRB (http://irb.psu.edu).

Not applicable.

5.3.3.2 Assent of subjects who are not yet adults

Indicate whether assent will be obtained from all, some, or none of the children. If assent will be obtained from some children, indicate which children will be required to assent. When assent of children is obtained describe whether and how it will be documented.

Not applicable.

6.0 HIPAA Research Authorization and/or Waiver or Alteration of Authorization

This section is about the access, use or disclosure of Protected Health Information (PHI). PHI is individually identifiable health information (i.e., health information containing one or more 18 identifiers) that is transmitted or maintained in any form or medium by a Covered Entity or its Business Associate. A Covered Entity is a health plan, a health care clearinghouse or health care provider who transmits health information in electronic form. See the "Investigator Manual (HRP-103)" for a list of the 18 identifiers. HRP-103 can be accessed by clicking the Library link in CATS IRB (http://irb.psu.edu).

If requesting a waiver/alteration of HIPAA authorization, complete sections 6.2 and 6.3 in addition to section 6.1. The Privacy Rule permits waivers (or alterations) of authorization if the research meets certain conditions. Include only information that will be accessed with the waiver/alteration.

6.1 Authorization and/or Waiver or Alteration of Authorization for the Uses and Disclosures of PHI

Check all that apply:

X **Not applicable, no identifiable protected health information (PHI) is accessed, used or disclosed in this study.** *[Mark all parts of sections 6.2 and 6.3 as not applicable]*

☐ **Authorization will be obtained and documented as part of the consent process.** *[If this is the only box checked, mark sections 6.2 and 6.3 as not applicable]*

☐ **Partial waiver is requested for recruitment purposes only (Check this box if patients' medical records will be accessed to determine eligibility before consent/authorization has been obtained).** *[Complete all parts of sections 6.2 and 6.3]*

☐ **Full waiver is requested for entire research study (e.g., medical record review studies).** *[Complete all parts of sections 6.2 and 6.3]*

☐ **Alteration is requested to waive requirement for written documentation of authorization (verbal authorization will be obtained).** *[Complete all parts of sections 6.2 and 6.3]*

6.2 Waiver or Alteration of Authorization for the Uses and Disclosures of PHI

6.2.1 Access, use or disclosure of PHI representing no more than a minimal risk to the privacy of the individual

6.2.1.1 Plan to protect PHI from improper use or disclosure

Include the following statement as written – DO NOT ALTER OR DELETE unless this section is not applicable because the research does not involve a waiver of authorization. If the section is not applicable, remove the statement and indicate as not applicable.

Not applicable

6.2.1.2 Plan to destroy identifiers or a justification for retaining identifiers

Describe the plan to destroy the identifiers at the earliest opportunity consistent with the conduct of the research. Include when and how identifiers will be destroyed. If identifiers will be retained, provide the legal, health or research justification for retaining the identifiers.

Not applicable

6.2.2 Explanation for why the research could not practicably be conducted without access to and use of PHI

Provide an explanation for why the research could not practicably be conducted without access to and use of PHI.

Not applicable

6.2.3 Explanation for why the research could not practicably be conducted without the waiver or alteration of authorization

Provide an explanation for why the research could not practicably be conducted without the waiver or alternation of authorization.

Not applicable

6.3 Waiver or alteration of authorization statements of agreement

By submitting this study for review with a waiver of authorization, you agree to the following statement – DO NOT ALTER OR DELETE unless this section is not applicable because the research does not involve a waiver or alteration of authorization. If the section is not applicable, remove the statement and indicate as not applicable.

Not applicable

7.0 Study Design and Procedures

7.1 Study Design

Describe and explain the study design.

A two-period randomized crossover trial will be conducted. Participants will be randomized to receive each treatment for 6 weeks followed by a minimum 4-week wash-out period. During the peanut treatment, participants will consume one ounce per day (28 g) of peanuts as an evening snack. The control treatments will be an isocaloric high carbohydrate snack (crackers + spread) consumed after the evening meal. The peanuts and control foods will be provided to the participants every two weeks during the treatment periods; these foods will be purchased from one of the local supermarkets. Participants will be given instructions about when to consume the foods.

Fasting blood glucose, fructosamine, insulin, weight, lipids and lipoproteins, central and peripheral blood pressure and arterial stiffness will be measured at the beginning and the end of each treatment period. Fecal samples will be provided at the beginning and the end of each treatment period for assessment of the microbiome. A 24-hour dietary recall will be completed at the beginning and end of each diet to determine how consuming the evening snack influences overall dietary intake (including calorie and macronutrient intake and overall diet quality).

7.2 Study Procedures

Provide a description of all research procedures being performed and when they are being performed (broken out by visit, if applicable), including procedures being performed to monitor subjects for safety or minimize risks. Include any long-term follow-up procedures and data collection, if applicable.

Describe where or how you will be obtaining information about subjects (e.g., medical records, school records, surveys, interview questions, focus group topics, audio or video recordings, data collection forms, and collection of specimens through invasive or non-invasive procedures to include the amount to be collected and how often). Add any data collection instruments that will be seen by subjects to your study in CATS IRB (http://irb.psu.edu) in the "Supporting Documents" page.

7.2.1 EXAMPLE: Visit 1 or Day 1 or Pre-test, etc. (format accordingly)

Provide a description as defined above and format accordingly.

Screening: The clinical visit will consist of filling out forms (informed consent, medical history, personal information); measuring height and weight so that BMI can be calculated; and measuring blood pressure to determine eligibility. If blood pressure is >140/90 mmHg at screening the individual will require written approval from their Primary Care Physician prior to enrolling the study. Women of child bearing potential will provide a urine sample for a pregnancy test. If after these measurements, it is determined that the subject is still eligible, a blood sample will be taken and a complete blood count, including liver and kidney function and a blood lipid panel will be performed (approximately 19 mls of blood or ~1.25 tablespoon will be taken). If the initial blood draw is unsuccessful it may need to be repeated, with permission from the participant. In addition, if a potential participant takes thyroid medicine they must provide a current (within 6 months) lab test. If they do not have one, an extra 3.5 ml (0.2 Tbsp) of blood will be taken to conduct a thyroid test. If all eligibility criteria are met, participants will be scheduled for their baseline measurements. Baseline visits typically occur within 1-2 weeks following the screening appointment.

7.2.2 EXAMPLE: Visit 2 or Day 2 or Post-test, etc. (format accordingly)

Provide a description as defined above and format accordingly.

Baseline and endpoint visits (8 total):
At the beginning and end of each diet period, two fasting blood samples will be collected (separated by at least 24 hours) for analysis of biochemical endpoints. Body weight will be taken

and vascular health assessments using the *SphygmoCor* will be performed at the beginning and end of each diet period. Participants will also complete a fecal collection at the beginning and end of each treatment period. Participants will complete a 24-hour dietary recall at the beginning and end of each treatment period.

Plasma/serum analysis: In addition to the blood taken at screening, 12 hour fasting blood samples also will be taken on two consecutive days at the beginning and end of each treatment period for a total of 8 times. Approximately 60 ml (about 4 Tbsp) will be collected across the two visits (30 ml per day). A typical American Red Cross blood donation is 1 pint (500 ml). Blood may be analyzed for the following: blood lipids and lipoproteins, glucose and insulin, and Fructosamine.

Central Blood Pressure and Augmentation Index: Following a 5-minute rest period, brachial artery systolic and diastolic blood pressure will be measured in the left arm using an automated blood pressure cuff. The cuff will reinflate and obtain a pulse wave form. Central blood pressure and wave reflection characteristics (augmentation index) will then be derived from the pressure waveforms using a validated transfer function with a SphygmoCor System (AtCor Medical, Sydney, Australia). This test will be performed in triplicate.

Pulse Wave Velocity: Arterial stiffness will be assessed by calculating the pulse wave velocity (PWV) between the carotid and femoral arteries while in the supine position. A cuff will be placed on the participant's thigh. The cuff will inflate during the test to record the pulse waveform in the femoral artery. A simultaneous measurement of the carotid artery pressure waveform will be obtained by an applanation tonometry sensor manually held in place above the carotid artery. PWV will subsequently be calculated by dividing the linear distance between the carotid and femoral sites by the transit time using the SphygmoCor system (AtCor Medical, Sydney Australia). This measurement will be performed in triplicate.

Fecal collection: At the beginning and end of each treatment period, participants will be asked to collect a stool sample (~50 g). They will be provided with a stool sample kit and detailed instructions for collection of a clean sample.

Dietary intake: The 24-hour recall will be administered through the Automated Self Administered 24-Hour (ASA24®) Dietary Assessment Tool. This is an online system where participants will provide information about all foods, beverages and supplements consumed during the previous day. No identifying information is uploaded to this system, participant ID numbers are used to identify the 24-hour records. Participants will have the option of the completing the 24-hour recall at home or at the visit. This system generates food group and nutrient data from the 24- hour recalls. These data will be used for calculation of diet quality.

Daily monitoring form: Participants will complete daily monitoring forms regarding consumption of test foods, changes in medication or health during the study. When they pick up their tests food biweekly, they will be provided with the daily monitoring forms and asked to return the completed forms the next time they pick up food.

7.3 Duration of Participation

Describe the duration of an individual subject's participation in the study.

Each participant will be involved in the study for approximately 16 weeks; two treatment periods each lasting 6 weeks, separated by a ≥ 4 week break. Participants will be expected to pick up the test foods

biweekly at the diet center on campus. At the beginning and end of each diet period, data collection (described above) will occur.
Total time for study visits, after the initial screening is approximately 6 hours. Times may vary and females will require an additional 5 minutes for a urine pregnancy test a baseline and the end of each diet period. The following is an estimate of the amount of time participants will spend in study activities:

- Screening appointment:
  - Day 1: Forms, blood pressure, weight, height, blood draw – 45-60 minutes
    - (pregnancy testing: females only – 5 minutes)
- Beginning of treatment period 1 and 2
  - Day 1: blood draw, weight, PWA, PWV – 60 minutes
    - (pregnancy testing: females only – 5 minutes)
  - Day 2: blood draw – 30 minutes
- End of treatment period 1 and 2:
  - Day 1: blood draw, weight, PWA, PWV – 60 minutes
    - (pregnancy testing: females only – 5 minutes)
  - Day 2: blood draw – 30 minutes
- Picking up food, fecal collections, and completing 24-hour diet recalls : ~ 5 hours

Total time for clinic and diet center visits from the beginning to the end of the study ~11 hours

8.0 Subject Numbers and Statistical Plan

8.1 Number of Subjects

Indicate the total number of subjects to be accrued.

If applicable, distinguish between the number of subjects who are expected to be enrolled and screened, and the number of subjects needed to complete the research procedures (i.e., numbers of subjects excluding screen failures.)

Approximately 135 subjects will complete the screening process for this study; of those we anticipate 59 subjects to be eligible A total of 45 participants will complete the study. To achieve this, we will likely need to randomize 59 subjects assuming a 30% drop out rate.

8.2 Sample size determination

If applicable, provide a justification of the sample size outlined in section 8.1 – to include reflections on, or calculations of, the power of the study.

To provide 80% power ($p<0.05$) to detect a minimum 10 mg/dL difference in fasting glucose between the treatments, 45 participants are required (standard deviation of 23.4mg/dL). To account for a 30% drop-out rate, 59 subjects will be randomized. Completion of 45 subjects will also provide 80% power ($p<0.05$) to detect a minimum 11 mg/dL (standard deviation 25.9 mg/dL) difference between the treatment in LDL-cholesterol, and a 4.5 mmHg difference in systolic blood pressure (standard deviation 11 mmHg).

8.3 Statistical methods

Describe the statistical methods (or non-statistical methods of analysis) that will be employed.

The normality of the data will be tested before performing analyses, and transformations will be made if needed. Mixed effect models will be used to determine between-group changes over time and between group differences in mean values following the treatments. Treatment will be included as a fixed effect. Subject will be included as a random effect.

9.0 Confidentiality, Privacy and Data Management

For research being conducted at Penn State Hershey or by Penn State Hershey researchers only, the research data security and integrity plan is submitted using "HRP-598 – Research Data Plan Review Form Application Supplement", which is available in the Library in CATS IRB (http://irb.psu.edu). Refer to Penn State College of Medicine IRB's "Standard Operating Procedure Addendum: Security and Integrity of Human Research Data", which is available on the IRB's website. **In order to avoid redundancy, for this section state "See the Research Data Plan Review Form" in section 9.0 if you are conducting Penn State Hershey research and move on to section 10.**

For all other research, in the sections below, describe the steps that will be taken to secure the data during storage, use and transmission.

9.1 Confidentiality

9.1.1 Identifiers associated with data and/or specimens

List the identifiers that will be included or associated with the data and/or specimens in any way (e.g., names, addresses, telephone/fax numbers, email addresses, dates (date of birth, admission/discharge dates, etc.), medical record numbers, social security numbers, health plan beneficiary numbers, etc.).

If no identifiers will be included or associated with the data in any way, whether directly or indirectly, please indicate this instead.

The study data and/or specimens will not contain identifiable information. Names, addresses, telephone numbers, email addresses, date of birth, and visit dates will be linked to data and specimens via a code break list. Once enrolled in the study, all data collection will be performed under an assigned study ID# that is known only to the principal investigators, study coordinators and CRC staff (for purposes of blood collection and safety). These are the only persons able to connect the participant's identifiable information.

9.1.1.1 Use of Codes, Master List

If identifiers will be associated with the data and/or specimens (as indicated in section 9.1.1 above), describe whether a master record or list containing a code (i.e., code number, pseudonyms) will be used to separate the data collected from identifiable information, where that master code list will be stored, who will have access to the master code list, and when it will be destroyed.

If identifiers are included or associated with the data as described in section 9.1.1 above, but no master record or list containing a code will be used, it will be assumed by the IRB that the investigator plans to directly link the identifiers with the data.

A master list containing a study ID number and participant's identity will be used. This will be stored on a central, password protected computer file or in locked study files located in locked research offices of the principal

investigators.

No data containing study ID#'s (code numbers) will be stored with the master list. Files will be maintained in locked file drawers or in password protected files to ensure security. Upon completion of data collection, only the investigators and study coordinator will have access to the list. This list will be destroyed 3 years after publication of the study results.

9.1.2 Storage of Data and/or Specimens

Describe where, how and for how long the data (hardcopy (paper) and/or electronic data) and/or specimens will be stored. NOTE: Data can include paper files, data on the internet or websites, computer files, audio/video files, photographs, etc. and should be considered in the responses. Refer to the "Investigator Manual (HRP-103)" for information about how long research records must be stored following the completion of the research prior to completing this section. HRP-103 can be accessed by clicking the Library link in CATS IRB (http://irb.psu.edu).

Please review Penn State's Data Categorization Project for detailed information regarding the appropriate and allowable storage of research data collected according to Penn State Policy AD71. Although the IRB can impose greater confidentiality/security requirements (particularly for sensitive data), the IRB cannot approve storage of research data in any way or using any service that is not permissible by Penn State Policy AD71.

Data will be stored in password protected computer files, locked file cabinets, locked offices, and using an identification coding system. Data will be stored for 3 years after the research has been published.

Consent forms will be stored in a locked office in a locked filing cabinet. Consent forms will stored for a least 3 years after the completion of the research.

9.1.3 Access to Data and/or Specimens

Identify who will have access to the data and/or specimens. This information should not conflict with information provided in section 9.1.1.1 regarding who has access to identifiable information, if applicable.

The principal investigators, co-investigator, study coordinators and trained study personnel will have access to data and specimens.

9.1.4 Transferring Data and/or Specimens

If the data and/or specimens will be transferred to and/or from outside collaborators, identify the collaborator to whom the data and/or specimens will be transferred and how the data and/or specimens will be transferred. This information should not conflict with information provided in section 9.1.1.1 regarding who has access to identifiable information, if applicable.

After collection, serum and plasma are transferred to ~1 mL aliquots – these vials contain only the participants study ID #, sample type (serum or plasma) and time point. The vials are then boxed and stored in a locked -80 degree freezer until all data collection is complete. Fecal samples will also be stored in a locked -80 degree freezer and the vials will contain no identifying information. Once the study is complete the samples will be sorted and

shipped on dry ice via FedEx or a Quest Courier to the following sites for analysis: (No identifying information is provided with the
samples)
Serum/Plasma:
- Quest diagnostics, 875 Greentree Rd., Pittsburgh, PA
Fecal samples:
- Wright Labs LLC, 419 14th Street, Huntingdon PA 16652

9.2 Subject Privacy

This section must address subject privacy and NOT data confidentiality.

Indicate how the research team is permitted to access any sources of information about the subjects.

Describe the steps that will be taken to protect subjects' privacy interests. "Privacy interest" refers to a person's desire to place limits on whom they interact with or to whom they provide personal information.

Describe what steps you will take to make the subjects feel at ease with the research situation in terms of the questions being asked and the procedures being performed. "At ease" does not refer to physical discomfort, but the sense of intrusiveness a subject might experience in response to questions, examinations, and procedures.

Once enrolled in the study, all data collection will be performed under an assigned study ID# that is known only to the principal investigators, co-investigators, study coordinators and CRC staff (for purposes of blood collection and safety). These are the only persons able to connect the participant's identifiable information. In addition, all study personnel have conducted IRB training and are aware of the importance involved with maintaining privacy and confidentiality when interacting with participants in any setting.

All clinical visits are conducted at the CRC by highly trained clinical staff. The CRC maintains the same level of privacy and sterility that is expected in a hospital setting and all clinical assessments are conducted within private rooms.

10.0 Data and Safety Monitoring Plan

This section is required when research involves more than Minimal Risk to subjects. As defined in "SOP: Definitions (HRP-001)", available in the Library in CATS IRB (http://irb.psu.edu), Minimal Risk is defined as the probability and magnitude of harm or discomfort anticipated in the research that are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests. For research involving prisoners, Minimal Risk is the probability and magnitude of physical or psychological harm that is normally encountered in the daily lives, or in the routine medical, dental, or psychological examination of healthy persons. **Please complete the sections below if the research involves more than minimal risk to subjects OR indicate as not applicable.**

10.1 Periodic evaluation of data

Describe the plan to periodically evaluate the data collected regarding both harms and benefits to determine whether subjects remain safe.

Not applicable

10.2 Data that are reviewed

Describe the data that are reviewed, including safety data, untoward events, and efficacy data.

Not applicable

10.3 Method of collection of safety information

Describe the method by which the safety information will be collected (e.g., with case report forms, at study visits, by telephone calls and with subjects).

Not applicable

10.4 Frequency of data collection

Describe the frequency of data collection, including when safety data collection starts.

Not applicable

10.5 Individuals reviewing the data

Identify the individuals who will review the data. The plan might include establishing a data and safety monitoring committee and a plan for reporting data monitoring committee findings to the IRB and the sponsor.

Not applicable

10.6 Frequency of review of cumulative data

Describe the frequency or periodicity of review of cumulative data.

Not applicable

10.7 Statistical tests

Describe the statistical tests for analyzing the safety data to determine whether harms are occurring.

Not applicable

10.8 Suspension of research

Describe any conditions that trigger an immediate suspension of research.

Not applicable

11.0 Risks

List the reasonably foreseeable risks, discomforts, hazards, or inconveniences to the subjects related the subjects' participation in the research. For each potential risk, describe the probability, magnitude, duration, and reversibility. Consider all types of risk including physical, psychological, social, legal, and economic risks. If applicable, indicate which procedures may have risks to the subjects that are currently unforeseeable. If applicable, indicate which procedures may have risks to an embryo or fetus should the subject be or become pregnant. If applicable, describe risks to others who are not subjects.

Please keep in mind that loss of confidentiality is a potential risk when conducting human subject research and should be addressed as such.

Gastrointestinal symptoms:

Some participants may experience GI (stomach) upset from the changes to their diet with incorporation of the test foods; symptoms may include, but are not limited to, any of the following: constipation/diarrhea, nausea, and bloating. This will likely subside once the participant becomes accustomed to the study foods.

Food Allergies:
Individuals will be asked to report any food allergies during the telephone screen, however it is possible that an unknown food allergy may manifest during the study. This is most likely to occur within the first week of the treatment period. Each day participants will be asked to complete a daily monitoring form so that we may track any adverse events, including potential food allergies, and identify the source as soon as possible. In addition, we ask participants to please inform study staff immediately should any adverse events occur.

Blood Sampling:
Blood draws often cause mild pain, swelling or bleeding. There may be some bruising (blood under the surface of the skin), which can be minimized by pressing on the site after the needle is removed. There is also a slight chance of infection, dizziness or fainting. These risks will be minimized and most likely eliminated by having trained staff draw the blood in a clinical setting using sterile supplies. If dizziness or fainting occurs, the symptoms will be alleviated by having the participant lie flat with their feet raised. If these should occur, the participant may be asked to remain at the clinic until the nurses have checked the participant's blood pressure and are sure the participant is ok to leave.

SphygmoCor (Pulse Wave Analysis and Pulse Wave Velocity):
There are no known risks associated with these measurements. The sensation of pressure from the blood pressure cuff or hand-held probe may be uncomfortable. There is a possibility for red blotching or mild bruising (petechiae) appearing on the skin above and below the location of the blood pressure cuff. Studies indicate that petechiae are rare (occurring in less than ½ of 1% of patients) and it is typically not uncomfortable and does not require treatment.

Loss of Confidentiality:
There is always a potential for loss of confidentiality despite our best efforts. To prevent this from occurring all records are coded with a unique ID number and no names are used. Records containing names or other identifying information are kept under lock at the PI's research office. All records associated with an individual's participation in the study will be subject to the usual confidentiality standards applicable to medical records. In the event of publication of this research, no personal identifying information will be disclosed.

Fecal Sample Collection:
Some participants may experience a certain level of embarrassment or discomfort from being asked to collect stool samples.

12.0 Potential Benefits to Subjects and Others

12.1 Potential Benefits to Subjects

Describe the potential benefits that individual subjects may experience from taking part in the research. If there is no direct benefit to subjects, indicate as such. Compensation is not considered a benefit. Compensation should be addressed in section 14.0.

Participants will receive their screening laboratory results, including a complete blood count, interpretation of liver and kidney function, and blood lipid values, at no cost.

12.2 Potential Benefits to Others

Include benefits to society or others.

The findings of this study will be applicable to the 84 million adults living with pre-diabetes in the US, and if shown to improve glycemic control the results may be extrapolated to the 30 million adults living with diabetes in the U.S.[1]. This equates to approximately one third of the U.S. population, which demonstrates the substantial public health burden attributable to pre-diabetes and diabetes. Further demonstrating the critical need for strategies to improve glycemic control is data showing that 46% of adults with diabetes have suboptimal glycemic control[1]. This novel study will empirically test the hypothesis that nighttime peanut consumption improves fasting glucose levels, and thus if supported this non-pharmaceutical treatment strategy is likely to have substantial clinical and public health implications. The findings of this research will be published in peer reviewed journals and these papers will likely be cited by clinical management guidelines and inform dietary recommendations. Therefore, the findings of this research are likely to inform clinical practice and dietary guidelines for individuals with impaired fasting glucose.

13.0 Sharing Results with Subjects

Describe whether results (study results or individual subject results, such as results of investigational diagnostic tests, genetic tests, or incidental findings) will be shared with subjects or others (e.g., the subject's primary care physicians) and if so, describe how it will be shared.

Screening results are provided to all potential participants (regardless of their eligibility status) within 2 weeks of their screening appointment. All screening results are reviewed by the Nurse Practitioner or Physician at the Clinical Center. Should any abnormal lab values be identified that warrant further evaluation the individual will be contacted (by the Study Coordinator) and asked to schedule a visit with their primary care physician. Individual results following each treatment period may be provided to participants upon request following completion of all study related data collection and analyses.

14.0 Subject Stipend (Compensation) and/or Travel Reimbursements

Describe the amount and timing of any subject stipend/payment or travel reimbursement here. If there is no subject stipend/payment or travel reimbursement, indicate as not applicable.

If course credit or extra credit is offered to subjects, describe the amount of credit and the available alternatives. Alternatives should be equal in time and effort to the amount of course or extra credit offered.

If an existing, approved student subject pool will be used to enroll subjects, please indicate as such and indicate that course credit will be given and alternatives will be offered as per the approved subject pool procedures.

For their time and participation in the study participants will receive monetary compensation of $400, prorated as follows and paid at the completion of their participation in the study:

Completion of first treatment period = $100
Completion of second treatment period = $300
The total of $400 will be paid at the completion of the participant's involvement with the study.

Participants may not be eligible for compensation if determined that specific work or visa laws conflict.

15.0 Economic Burden to Subjects

15.1 Costs

Describe any costs that subjects may be responsible for because of participation in the research.

The participants will not bear any costs due to their participation in the study.

15.2 Compensation for research-related injury

If the research involves more than Minimal Risk to subjects, describe the available compensation in the event of research related injury.

If there is no sponsor agreement that addresses compensation for medical care for research subjects with a research-related injury, include the following text as written - DO NOT ALTER OR DELETE:
It is the policy of the institution to provide neither financial compensation nor free medical treatment for research-related injury. In the event of injury resulting from this research, medical treatment is available but will be provided at the usual charge. Costs for the treatment of research-related injuries will be charged to subjects or their insurance carriers.

For sponsored research studies with a research agreement with the sponsor that addresses compensation for medical care for research-related injuries, include the following text as written - DO NOT ALTER OR DELETE:
It is the policy of the institution to provide neither financial compensation nor free medical treatment for research-related injury. In the event of injury resulting from this research, medical treatment is available but will be provided at the usual charge. Such charges may be paid by the study sponsor as outlined in the research agreement and explained in the consent form.

Not applicable – the research does not involve more than minimal risk.

16.0 Resources Available

16.1 Facilities and locations

Identify and describe the facilities, sites and locations where recruitment and study procedures will be performed.

If research will be conducted outside the United States, describe site-specific regulations or customs affecting the research, and describe the process for obtaining local ethical review. Also, describe the principal investigator's experience conducting research at these locations and familiarity with local culture.

Penn State University Clinical Research Center -The clinical aspects of this study will be conducted at the Clinical Research Centre (CRC) on the University Park campus of the Pennsylvania State University. The CRC is a purpose-built research unit that supports human clinical research trials, and is fully equipped with exam rooms, invasive and general procedure rooms and five hospital-style bedrooms with bathrooms. There is also a specimen processing room with refrigerated and unrefrigerated centrifuges for preparation of samples. The study investigators will work closely with experienced CRC staff (physicians, nurse practitioners, registered nurses and research technologists) to optimize and facilitate the research protocol. The principal investigators, co-investigator, and project coordinators are experienced with conducting research at this location and have conducted multiple clinical trials at this location previously.

The Penn State Metabolic Diet Study Center is a state-of-the-art facility consisting of a spacious dining area, a pantry and a fully-equipped kitchen specifically designed for nutrition studies. In addition, this area is available for small group meetings with study participants and counseling/information exchange with small groups of individuals.

16.2 Feasibility of recruiting the required number of subjects

Indicate the number of potential subjects to which the study team has access. Indicate the percentage of those potential subjects needed for recruitment.

Given the wide age range and broad recruitment criteria we believe these methods, which have been successful in the past, will enable us to recruit the necessary participants within the appropriate time frame.

16.3 PI Time devoted to conducting the research

Describe how the PI will ensure that a sufficient amount of time will be devoted to conducting and completing the research. Please consider outside responsibilities as well as other on-going research for which the PI is responsible.

The Principal Investigators will be responsible for assuring through personal contact between the coinvestigator, clinical staff and coordinators that each individual clearly understands and accepts the obligations incurred in the undertaking of this clinical trial.
The Principal Investigators will ensure that the clinical staff fully understand the nature of the protocol and the requirements for an adequate and well-controlled study; the obligation to conduct the clinical investigation in accordance with the applicable federal regulations; the obligation to obtain informed consent in accordance with 21 CFR Part 50; the obligation to obtain IRB review and approval of a clinical investigation before the investigation may be initiated and to ensure continuing review of the study by the IRB in accordance with 21 CFR Part 56.

16.4 Availability of medical or psychological resources

Describe the availability of medical or psychological resources that subject might need as a result of their participation in the study, if applicable.

A clinician is always present during clinical testing. Highly trained nursing staff will perform clinical assessments. Should an individual require psychological services they will be referred to the on campus clinic: Psychological Clinic, 314 Moore Bldg., University Park, Phone: 865-2191.

16.5 Process for informing Study Team

Describe the training plans to ensure members of the research team are informed about the protocol and their duties, if applicable.

All study staff will be required to complete the Human Participant Training and Bloodborne Pathogen Training as mandated by the Pennsylvania State University Office of Research Protections. In addition, as part of the initial training for this study, all staff members (e.g. project managers, research coordinators, assistants, and Clinical Research Center [CRC] nursing staff) will conduct an initial project start-up meeting to review the scientific protocol and ensure all study procedures are in place.

17.0 Other Approvals

17.1 Other Approvals from External Entities

Describe any approvals that will be obtained prior to commencing the research (e.g., from cooperating institutions, community leaders, schools, external sites, funding agencies).

IBC approval will be obtained for the collection and analysis of blood and fecal samples.

17.2 Internal PSU Committee Approvals

Check all that apply:

☐ Anatomic Pathology – Hershey only – Research involves the collection of tissues or use of pathologic specimens. Upload a copy of HRP-902 - Human Tissue For Research Form on the "Supporting Documents" page in CATS IRB. This form is available in the CATS IRB Library.

☐ Animal Care and Use – All campuses – Human research involves animals and humans or the use of human tissues in animals

X Biosafety – All campuses – Research involves biohazardous materials (human biological specimens in a PSU research lab, biological toxins, carcinogens, infectious agents, recombinant viruses or DNA or gene therapy).

☐ Clinical Laboratories – Hershey only – Collection, processing and/or storage of extra tubes of body fluid specimens for research purposes by the Clinical Laboratories; and/or use of body fluids that had been collected for clinical purposes, but are no longer needed for clinical use. Upload a copy of HRP-901 - Human Body Fluids for Research Form on the "Supporting Documents" page in CATS IRB. This form is available in the CATS IRB Library.

X Clinical Research Center (CRC) Advisory Committee – All campuses – Research involves the use of CRC services in any way.

☐ Conflict of Interest Review – All campuses – Research has one or more of study team members indicated as having a financial interest.

☐ Radiation Safety – Hershey only – Research involves research-related radiation procedures. All research involving radiation procedures (standard of care and/or research-related) must upload a copy of HRP-903 - Radiation Review Form on the "Supporting Documents" page in CATS IRB. This form is available in the CATS IRB Library.

☐ IND/IDE Audit – All campuses – Research in which the PSU researcher holds the IND or IDE or intends to hold the IND or IDE.

☐ Scientific Review – Hershey only – All investigator-written research studies requiring review by the convened IRB must provide documentation of scientific review with the IRB submission. The scientific review requirement may be fulfilled by one of the following: (1) external peer-review process; (2) department/institute scientific review committee; or (3) scientific review by the Clinical Research Center Advisory committee. NOTE: Review by the Penn State Hershey Cancer Institute Scientific Review Committee is required if the study involves cancer prevention studies or cancer patients, records and/or tissues. For more information about this requirement see the IRB website at: http://www.pennstatehershey.org/web/irb/home/resources/investigator

18.0 Multi-Site Research

If this is a multi-site study (i.e., the study will be conducted at other institutions each with its own principal investigator) and you are the lead investigator, describe the processes to ensure communication among sites in the sections below.

18.1 Communication Plans

Describe the plan for regular communication between the overall study director and the other sites to ensure that all sites have the most current version of the protocol, consent document, etc. Describe the process to ensure all modifications have been communicated to sites. Describe the process to ensure that all required approvals have been obtained at each site (including approval by the site's IRB of record). Describe the process for communication of problems with the research, interim results and closure of the study.

Not applicable

18.2 Data Submission and Security Plan

Describe the process and schedule for data submission and provide the data security plan for data collected from other sites. Describe the process to ensure all engaged participating sites will safeguard data as required by local information security policies.

Not applicable

18.3 Subject Enrollment

Describe the procedures for coordination of subject enrollment and randomization for the overall project.

Not applicable

18.4 Reporting of Adverse Events and New Information

Describe how adverse events and other information will be reported from the clinical sites to the overall study director. Provide the timeframe for this reporting.

Not applicable

18.5 Audit and Monitoring Plans

Describe the process to ensure all local site investigators conduct the study appropriately. Describe any on-site auditing and monitoring plans for the study.

Not applicable

19.0 Adverse Event Reporting

19.1 Reporting Adverse Reactions and Unanticipated Problems to the Responsible IRB

By submitting this study for review, you agree to the following statement – DO NOT ALTER OR DELETE:

In accordance with applicable policies of The Pennsylvania State University Institutional Review Board (IRB), the investigator will report, to the IRB, any observed or reported harm (adverse event) experienced by a subject or other individual, which in the opinion of the investigator is determined to be (1) unexpected; and (2) probably related to the research procedures. Harms (adverse events) will be submitted to the IRB in accordance with the IRB policies and procedures.

20.0 Study Monitoring, Auditing and Inspecting

20.1 Auditing and Inspecting

By submitting this study for review, you agree to the following statement – DO NOT ALTER OR DELETE:

The investigator will permit study-related monitoring, audits, and inspections by the Penn State quality assurance program office(s), IRB, the sponsor, and government regulatory bodies, of all study related documents (e.g., source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g., pharmacy, diagnostic laboratory, etc.).

21.0 Future Undetermined Research: Data and Specimen Banking

If this study is collecting identifiable data and/or specimens that will be banked for future undetermined research, please describe this process in the sections below. This information should not conflict with information provided in section 9.1.1 regarding whether or not data and/or specimens will be associated with identifiers (directly or indirectly).

21.1 Data and/or specimens being stored

Identify what data and/or specimens will be stored and the data associated with each specimen.

Blood (serum/plasma) may be stored for future testing.
Fecal Samples: Analysis of microbial composition and identification of metabolites

21.2 Location of storage

Identify the location where the data and/or specimens will be stored.

Chandlee Lab: Room 318 in a locked -80 degree freezer

21.3 Duration of storage

Identify how long the data and/or specimens will be stored.

Specimens will be destroyed 3 years after publication of results, unless permission has been granted to keep. If permission to keep the samples has been granted, the samples may be stored indefinitely or until the integrity of the sample is comprised.

21.4 Access to data and/or specimens

Identify who will have access to the data and/or specimens.

Specimens will be boxed, labeled by sample type, study name, and dates of collection, and stored in a locked -80 degree freezer. Samples will only be accessible to designated staff and students for purposes outlined in this proposal.

21.5 Procedures to release data or specimens

Describe the procedures to release the data and/or specimens, including: the process to request a release, approvals required for release, who can obtain data and/or specimens, and the data to be provided with the specimens.

All specimens will be coded with non-identifiable labels. Participants may elect to make their samples available for additional analyses by study collaborators.

21.6 Process for returning results

Describe the process for returning results about the use of the data and/or specimens.

No specimens are returned to participants.

22.0 References

List relevant references in the literature which highlight methods, controversies, and study outcomes.

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