Informed Consent Form

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NC STATE UNIVERSITY

Informed Consent for Participation in Research Guidance

Annex 5: Consent form
Version 4 06/01/2020

Blueberry
Absorption
Metabolism

NC STATE UNIVERSITY
Plants for Human Health INSTITUTE

NC RESEARCH CAMPUS

Title of Study: Establishing optimal nutritional quality of blueberries: *a proof of concept study to improve the nutritional quality of the average diet using common plant breeding and processing practices* (eIRB # 19138)
Principal Investigator: Dr. Colin D. Kay, cdkay@ncsu.edu, 704-250-5451
Funding Source: Foundation for Food and Agriculture Research (FFAR)
Faculty Point of Contact: Cheri Granillo, cdgranil@ncsu.edu, 704-250-5492

What are some general things you should know about research studies?
You are invited to take part in a research study. Your participation in this study is voluntary. You have the right to be a part of this study, to choose not to participate, and to stop participating at any time without penalty. The purpose of this research study is to gain a better understanding of how berries are processed by the human body. We will do this by feeding you berries or products with berries in them and measuring how your body processes those berries through blood and urine samples.

You are not guaranteed any personal benefits from being in this study. Research studies also may pose risks to those who participate. You may want to participate in this research because you like eating blueberries or are curious about how your body processes food. You may not want to participate in this research because you might be uncomfortable or get a bruise when your blood is drawn for research purposes.

Specific details about the research are contained below. If you do not understand something in this form, or at any time, you have questions about your participation in this research, do not hesitate to contact the researcher named above or the NC State IRB office. The IRB office's contact information is listed at the end of this form.

What is the purpose of this study?
The purpose of the study is to evaluate how berries are utilized by the body, in healthy human volunteers.

Am I eligible to be a participant in this study?
In order to be a participant in this study, you must agree to be in the study and meet the eligibility criteria that are listed in Appendix A and reviewed with the researcher.

What will happen if you take part in the study?
If you agree to participate in this study, you will be asked to do all of the following:

Timing	Participant Selection
Consent visit (½ hour) Location: 600 Laureate Way, Suite 1315, Kannapolis, NC 28081	• Opportunity to ask questions about the study; • Review and sign the consent form • Have your height and weight measured; • Fill out a medical history form; • Fill out a medication use survey.
Clinical screening visit (1 hour) Location: 500 Laureate Way, Suite 1315, Kannapolis, NC 28081	• Come to the appointment having not had anything to eat or drink for 10 hours; • Your height, weight and blood pressure will be measured; • Completion of Medical History and medication use questionnaire; • We will draw your blood once; • We will ask you to give us a urine sample. We will use this sample to assess general health and pregnancy status (if applicable).
	Preparation for each Study Period
The 7d before feeding visit and during study days	• Avoid berries, foods rich in berries and red or purple fruits and vegetables. Check Annex 2-"Food Exclusion and Alternatives List" • Avoid alcohol intake (*no more than 7* ***alcoholic drinks*** *per week for women and 14 drinks per week for men*) • Avoid caffeinated products [*a maximum of 2 medium cups (12-16 oz.) a day of* **tea** *and* **coffee**, but **no tea or coffee** one day before the feeding visit and on study visit days 1 and 2] *If you accidentally consume restricted foods, simply write this in the food intake diary and try to avoid the restricted foods in the future, or if it is within one week of the study visit, to repeat eating these foods on subsequent visits for consistency.*
48 hours (two days) prior to feeding visit	• Write down everything you eat and drink on a food intake record each day (template provided on Annex 3- "Food Intake Record") • Collect all the urine you generate each day into study provided collection containers (collection instructions on Annex 4- "Urine Collection Instructions")
Evening before clinical assessment	• Observe an overnight fast (for 10 hours prior to your visit, only drink water and do not eat anything)
	Study days (there are 4 study periods, each lasting 3 days. The study periods are separated by a 18-25 day interval)
Location: 500 Laureate Way, Kannapolis, Suite 1315, NC 28081	Day 1 (9 hour long visit) 1. Bring your food intake records and urine samples to the visit 2. Your resting blood pressure, height, and weight will be measured

	3. We will ask you to fill out a survey about your experiences while you've in the study, such as your health and if anything unexpected has happened. 4. We will take samples of blood and urine from you before you eat or drink anything. 5. We will ask you to add all your urine voids during this course of your 9 hour visit into a container we will provide to you. 6. You will be offered one of the following to consume: fresh berries, a berry protein bar, or a beverage. 7. You will then eat breakfast that we will give you. 8. After you've eaten, your blood will be taken 4 more times over the course of your 9 hour visit. 9. We will feed you lunch, dinner, and snacks. You will write down everything you eat and drink. 10. We will take the container where you were adding urine samples from you at the end of your 9 hour visit. 11. You will fill out a travel expense form before you leave if applicable. Day 2 (about a 1 hour visit) 12. Bring your food intake records and urine samples to the visit. 13. We will take a sample of blood from you before your eat or drink anything. 14. You will eat breakfast at the study site. You'll write down everything you eat and drink. 15. We will give you lunch, dinner, and snakes to take home and eat. 16. You will fill out a travel expense form before you leave. Day 3 (about a 1 hour visit) 1. Bring your food intake records and urine samples to the visit. 2. We will take a sample of blood from you before your eat or drink anything. 3. You will eat breakfast at the study site. You'll write down everything you eat and drink. 4. You will fill out a travel expense form before you leave.
11-18 days interval between each study period	• Consume any food you want; no restrictions are applicable during this time period.
End of the study (last study day)	• Participation compensation is arranged in person; • Exit questionnaire (optional) is answered in person or via email;

For a more detailed description of procedures summarized in the table refer to Appendix B.

The following procedures are experimental: we will ask you to consume one of the commercial blueberry varieties, or blueberry-rich protein bar or nutrient matched control beverage, and we will collect some sample of your blood and urine to analyze for blueberry components absorbed after consumption.

Risks and benefits

There are minimal risks related to the research procedures and the data generated from the research.

Some participants may experience pain and/or bruising from the blood draws regardless of method of collection. We will draw your blood with the needlestick blood collection method for most of your study visits. When you come for your 9-hour study visit, you get to choose how your blood is drawn from your body: needlestick or cannulation.

- With a needlestick venipuncture, a single needle will be inserted into a vein in your arm to collect blood. The needle is inserted and removed fairly quickly, but the disadvantage of this approach is that we will need you to have multiple needlesticks during your 9.5-hour study visits.
- With cannulation, a small tube ("cannula)" is inserted into a vein in your arm so that a needle can be inserted into the tube and draw blood from there. The initial procedure to place the tube is a bit more complicated than the needlestick. There is also a risk that the tube can become blocked. We will wash the tube between blood draws so it is clean each time we use it. The advantage, however, of cannulation is that you will only experience a needle poking into your skin once instead of multiple times if you choose the needlestick collection. Keep in mind that with this method, you will have a tube in your arm for maximum 9.5h. If the tube becomes blocked at any point, we will remove the tube and revert to needlestick venipuncture for the blood draws with your consent. The cannula should be accessed by lab or study personnel only. If the cannula becomes dislodged at any time throughout the day, you should return to the lab immediately. You cannot leave the NRI building, where the phlebotomy laboratory is located, while the cannula is in your arm.

Infection, excessive bleeding, clotting, and/or fainting from blood draws are also possible, although unlikely, in both blood draw methods. We are mitigating these risks by having licensed, experienced medical professionals draw your blood within current standards of care for blood draws and ensuring that you have something to eat after each fasting blood draw. We also will limit blood draw attempts to 2 per vein on your arm. If we are unsuccessful drawing blood from a vein in your arm, 1 additional. experienced medical professional will try the venipuncture one time, for a maximum of 3 attempts at the venipuncture per arm.

There is a risk that your body may react to some of the food that we will give you to consume. We do not expect this to happen because the food will be prepared in commercial grade kitchens using food safe practices. We are also excluding people from participating in the study that have food allergies or intolerance to salicylates, berries, or berry derived products as a precautionary measure.

There is a risk to privacy if our data is breeched due to the private health information and biospecimens that you are sharing with us. We are implementing data security measures appropriate to the sensitivity of your personal data. We are also committed to securely and permanently destroying your health data if you drop out of the study at any time for any reason. If you choose to complete the study, your identifiable information will be destroyed immediately following publication of the first manuscript from the study and or completion of the project grant.

There are no direct benefits to you participating in this study, You are, however, helping others to understand the nutritional value of berries.

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Right to withdraw your participation

You may stop participating in this study at any time for any reason. In order to stop your participation, please contact the study coordinator, Monique Carvalho de Santana, mcarval@ncsu.edu and 704-250-5451 or the faculty point of contact for this protocol, Cheri Granillo, cdgranil@ncsu.edu and 704-250-5492. If you choose to withdraw your consent and to stop participating in this research, you can expect that the research team will take out your information and biospecimens from their data set, securely destroy your data, and prevent future uses of your data for research purposes wherever possible. This is possible in some, but not all, cases. You will also still receive compensation for all of the research procedures you completed.

Confidentiality, personal privacy, and data management

Trust is the foundation of the participant/researcher relationship. Much of that principle of trust is tied to keeping your information private and in the manner that we have described to you in this form. The information that you share with us will be held in confidence to the fullest extent allowed by law. Protecting your privacy as related to this research is of utmost importance to us.

How we manage, protect, and share your data are the principal ways that we protect your personal privacy. Protecting your privacy as related to this research is of utmost importance to us. There are very rare circumstances related to confidentiality where we may have to share information about you. Your information collected in this research study could be reviewed by representatives of the University, research sponsors, or government agencies (for example, the FDA) for purposes such as quality control or safety. In other cases, we must report instances in which imminent harm could come to you or others.

All study records will be kept confidential. Hard-copy data will be stored in a locked cabinet in the PI's office which is also locked and accessible only by card access. Digital data will be stored in separate secure server locations on an NC State managed network and the files will be accessible only via account password protection and transferred via encrypted email on the NCSU web server.. All biological samples will be coded with a unique randomly generated identification number. Only the principal investigator, Dr. Colin D. Kay, will have access to the coded anonymized information. The study coordinator, Monique Carvalho de Santana, will be provided access to the data in the case of an emergency.

Data shared about you in this study will be de-identified. While we might be able to link your identity to your data at earlier stages in the research, when the research concludes, there will be no way your real identity will be linked to blood results or the data we publish. Study results will only be provided in a summarized fashion to our study sponsor and scholarly publications. No reference will be made in oral or written reports which could link you to the study.

Your de-identified blood and urine samples will be stored at the Plants for Human Health Institute of the North Carolina State University for a minimum of 3 and no more than 10 years from collection.

Compensation

For participation in this study, a $312 maximum compensation will be provided to you (in addition to travel reimbursement) calculated in proportion to the number of blood collections, urine collections, and food records you complete for the study. The breakdown is as follows:

- $5 for each 24-hours of urine collection samples
- $7 for each blood sample

- $4 for each 4-day food intake report

Compensation for participants who are H-1B visa holders and sponsored by NC State University is dependent upon the presentation of the below documents, or the participant can opt of receiving compensation to participate in this study:

- Copy of passport photo page
- Copy of entry stamp in passport
- Copy of I-797 approval notice with I-94 (Can be printed from: https://i94.cbp.dhs.gov/I94/#/home)
- Confirmation from sponsoring institution's Office of International Services indicating they are aware of the visitor's activity with NCSU and the payment s/he is receiving (University best practice).

However, H-1B visa holders who are sponsored by another Institution need to get the permission of their host Institution before participation and the compensation would be processed directly to the sponsoring Institution.
North Carolina State University does not authorize compensation to individuals under J-1 or F-1 visas. In this way, participation of J-1 and F-1 visa holders is voluntary.

You will be paid at the end of the study or when you withdraw from the study, whichever occurs first. If you choose to withdraw from the study prior to its completion, you will receive partial compensation based on the procedures undertaken during your participation.

Travel expense reimbursement will be paid up to a maximum of 40 miles at $0.575/mile per study day (day 1 through day 3 of each study period). If you will be taking public transit, you can be reimbursed for those fares by giving your fare receipts for each attendance to campus for research procedures (i.e., bus or train) to the research coordinator. Your trips will be logged at every visit day, and you can process payment at every day 3 of each study period, or at the end of your participation in the study (last day). Travel reimbursement can be provided for everyone, and visa holders need to present some documents depending on his/her visa status (See appendix D in the Consent Form).

For any compensation or travel expense reimbursement, you will need to share your social security number and bank account information to Dona Miller, the NCSU Administrative Support Specialist in the North Carolina Research Campus' administrative office. Her email is dona_miller@ncsu.edu and her phone number is 704-250-5449. The research team will provide you a form to complete and bring to Ms. Miller so that she can process the payment directly into your bank account or have a check issued and mailed to your home. Your banking information and social security number will not be shared or handled by any member of the research team.

Emergency medical treatment
If you are hurt or injured during the study session(s), the researcher will call 911 for necessary care. There is no provision for compensation or free medical care for you if you are injured as a result of this study.

What if you are an NCSU student?
Your participation in this study is not a course requirement and your participation or lack thereof, will not affect your class standing or grades at NC State.

What if you are an NCSU employee?

Your participation in this study is not a requirement of your employment at NCSU, and your participation or lack thereof, will not affect your job.

Sponsorship and Funding

This research is funded by the Foundation for Food and Agriculture Research (FFAR). This means that the sponsor is paying the research team for completing the research. The Foundation for Food and Agriculture Research (FFAR) is a unique federally funded, public-private partnerships to support innovative science addressing today's food and agriculture challenges. The researchers do not have a direct financial interest with the sponsor or in the final results of the study. If you would like more information, please ask the researcher listed in the first page of this form about the funding and sponsorship.

What if you have questions about this study?

If you have questions at any time about the study itself or the procedures implemented in this study, you may contact the research coordinator, Monique Carvalho de Santana, blueberrystudy@ncsu.edu, and (704) 250-5451, or the Faculty advisor Cheri Granillo, cdgranil@ncsu.edu, 704-250-5492.

What if you have questions about your rights as a research participant?

If you feel you have not been treated according to the descriptions in this form, or your rights as a participant in research have been violated during the course of this project, you may contact the NC State IRB (Institutional Review Board) Office. An IRB office helps participants if they have any issues regarding research activities. You can contact the NC State IRB Office via email at irb-director@ncsu.edu or via phone at (919) 515-8754.

	Participant Initials
1. Have you read the Participant Information Material?.....YES/NO	
2. Do you agree that you do not fall within the basic exclusion criteria listed for this research study (Appendix A)?.....YES/NO*	
3. Have you had an opportunity to discuss this study and ask questions; including the exclusion criteria and your responsibilities as a volunteer?.....YES/NO	
4. With whom have you discussed the information for this research study? _____	
5. Have you received sufficient information about the study?.....YES/NO	
6. Have you read the detailed description of the study procedures (Appendix B)?.....YES/NO	
7. Have you received satisfactory answers to all your questions? ……YES/NO	
8. Do you understand that you are free to withdraw from the study: At any time, without having to give a reason for withdrawing, without withdrawal affecting future participation in other research studies?.....YES/NO	

9. Do you agree to have blood samples collected from you either by single cannula or by a series of needle sticks (see Appendix C)?*.....YES/NO	
9.1 If you opt to have blood samples collected by single cannula, do you agree not to bend the arm in which the cannula is inserted for the entire period while it is in your arm?.....YES/NO	
9.2 If you opt to have blood samples collected by single cannula, do you agree to come back to the clinic (Human Research Core) every hour to have the cannula flushed with saline?.....YES/NO	
9.3 If you opt to have blood samples collected by single cannula, do you agree to allow the cannula to be accessed only by study personnel?.....YES/NO	
10. Are you aware that your personal information will be kept confidential?.....YES/NO	
11. Are you aware that your blood and urine samples will be stored anonymously at the Plants for Human Health Institute of the North Carolina State University for a minimum of 3 and no more than 10 years from collection?.....YES/NO	
12. Are you aware of the potential hazards of participating in this study such as momentary discomfort and/or bruising from the introduction of a needle into your forearm vein, and highly unlikely infection, excess bleeding, clotting, and/or fainting?.....YES/NO	
13. Will you inform the study coordinator or the clinical team of the start of any medication/medical changes while participating in the study*……..YES/NO	
14. Do you understand that all research is subject to inspection and audit? Although your records may be accessed for this purpose your personal information remains confidential.……..……YES/NO	
15. Do you agree to request travel reimbursement (for a maximum of 20 miles from the North Carolina Research Campus) with the North Carolina State University administrative office by yourself in case you decide to request it?..... YES/NO	
16. Do you agree to consume a control beverage of whey protein dissolved in water, corn syrup and vegetable oil?.....YES/NO*	
17. Do you agree to abstain from coffee or tea one day before and during the first and second study visit days? ……..YES/NO *In the case where these are consumed accidently, you are asked to simply write this in the food intake diary and try to avoid it in the future, or if its within one week of the study visit, to repeat it on subsequent visits for consistency*.	
18. Are you a visa holder?.....……..YES/NO If yes, which type of visa? ____	
18.1 Do you understand that compensation for your participation may depend on the type of visa that you hold?.....YES/NO	

19. Do you agree to request compensation for the study procedures with the North Carolina State University administrative office by yourself in case you decide to request it?.....YES/NO	
20. Do you agree to take part in the study entitled "**BAM (Blueberry Absorption Metabolism) Study: a study investigating the nutritional equivalence of fresh and processed berries**"?.....YES/NO*	
21. Would you like to have your contact information retained to be invited to participate in future studies?.....YES/NO	

* If you have said NO to the questions marked with "*" we are unable to accept you in this study.

Consent to Participate

By signing this consent form, I am affirming that I have read and understand the above information. All of the questions that I had about this research have been answered. I have chosen to participate in this study with the understanding that I may stop participating at any time without penalty or loss of benefits to which I am otherwise entitled. I am aware that I may revoke my consent at any time.

Participant's printed name_____

Participant's signature _____ **Date** _____

Investigator's signature _____ **Date** _____

Appendix A: Inclusion and Exclusion criteria

You can participate in this study if you want to be in the study AND if you:

- are a male or female adult between 25-65 years;
- are non-smoker nor vaping or dipping (i.e., tobacco chewing) users (or ex-smoker who ceased ≥ 6 months ago);
- present no allergies to berries, red apple, red orange, purple onion and broccoli;
- if you present no allergies to dairy products, specifically whey protein, fructose or salicylates;
- are generally healthy and without chronic diseases including cancer, type 1 and 2 diabetes;
- not be prescribed thyroid or hypoglycemic medication or hormone replacement therapy (HRT) (due to the likely concomitant effects that these medications cause on the primary endpoint in the study);
- have not been consuming any supplements* rich in berries (e.g. berry, cocoa, tea or coffee extracts) for at least a month before the study and willing to not consume it during the study;
- live within 40 miles from the North Carolina Research Campus (NCRC) campus;
- agree to restrict dietary intake of foods similar to berries or dietary supplements* containing extracts from berry, cocoa, coffee or tea, during the week before the study and study days;
- agree to comply with the study procedures involving the collection of urine and blood samples, and to record your dietary intake over 2 days before each berry feeding study day, and two days after the berry or berry products intake;
- have body mass index (BMI) from ≥18.5 to ≤ 30 ($lbs/in^2 x703$);
- have a successful (i.e., within normal range for healthy individuals) biochemical, hematological and urine analyses assessed by our clinical advisor.

You cannot participate in this study if you do not want to be in the study or:

- are a current smoker [vape and dip (i.e., tobacco chewing) users included], or ex-smoker ceasing < 6 months before recruitment;
- are pregnant or breastfeeding;
- have current or significant past medical history of vascular disease or medical conditions likely to affect the study measures i.e. vascular disease, circulatory (i.e. Reynaud's), diabetes, hepatic, renal, digestive, hematological, cancer, or thyroid disease;
- are fructose intolerant or have allergy to salicylates, dairy products, specifically whey protein, or to berries;
- are unprepared to adhere to dietary restrictions for 1 week preceding and during each berry or berry product feeding visit or unwilling to comply with the study procedures;
- are in parallel participation in another research project involving dietary diet and/or sampling of biological fluids/material;
- are on therapeutic diets or having experienced substantial weight loss (to be judged by clinical advisor) within 3 months of screening;
- are taking supplements* rich in berries (e.g. berry, cocoa, tea or coffee extracts), unwilling to cease intake during, and 1 month preceding the study, or unwilling to stop existing intake of other supplements* (minerals, vitamins, plant extracts, plant or animal oils, amino acids, energy drinks) or regular use of large-dose nutrient, herbal, and dietary supplements* during the past one to two weeks, or planning to use them during the study;
- are prescribed thyroid, hypoglycemic medication or HRT medication -other medications will be assessed for suitability by the clinical advisor;
- have donated blood in the last month;

- consume more than 1 and 2 drinks of alcohol per day for women and men, respectively, or more than 7 and 14 drinks per week for women and men, respectively (U.S. Department of Health and Human Services and U.S. Department of Agriculture Dietary guidelines 2015-2020);
- are currently on a weight-reducing plan or using weight-loss medications (e.g., selective serotonin reuptake inhibitors, steroids, Ritalin, appetite suppressants such as Diethylpropion or Amfepramone, and weight loss medications such as Alli, Xenical, Qsymia, Belviq, Contrave, and Saxenda), or planning to continue this treatment during the approximate 10-week period of the study;
- present abnormal biochemical, hematological or urinary results, and measurements considered to be counter-indicative for the study, including: kidney and liver function, fasting glucose (especially if indicative of diabetes), lipid abnormalities, full blood count;
- have BMI<18.5 or >30 ($lbs/in^2 x703$).

*A supplement or health supplement refers to any dietary ingredient which is consumed in a format which is extracted from a food or plant. For example, vitamins, minerals, amino acids, herbs or botanicals, or even components or extracts from plants or animals such as extracts from fruits or omega-3-fatty acids from fish are generally considered supplements. These are most often consumed as a powder, pill or beverage, like an energy shot or drink. You may consume vitamins or minerals or amino acids or protein drinks or bars consumed as a meal replacement as long as it is typical to your usual diet and you consume this regularly. In the case where these are consumed accidently, you are asked to simply write this in the food intake diary and try to avoid it in the future, or if its within one week of the study visit, to repeat it on subsequent visits for consistency.

Appendix B: ***Detailed description of text summarized in Table 1***

1. In the consent visit (½ hour) at the Plants for Human Health Institute (PHHI; North Carolina Research Campus, 600 Laureate Way; Kannapolis, NC 28081), you will be able to clarify any questions, it will be explained that volunteers will be given a list of foodstuffs to 'avoid' and/or 'limit', and alternatives to them during the wash-out week and visit days; the intake of tea and coffee will be limited to a combined intake of 2 medium cups (12-16 oz) per day during washout, but none on the day before the berry feeding visit, and the intake of alcohol will also be regulated based on the recommendations of the Food and Drug Administration (Annex 2- "Food Exclusion and Alternatives List"). You will also be required to refrain from taking supplements containing extracts of cocoa, coffee, tea or berries for at least 1 month prior to the assessment visits, and throughout the study. Volunteers will be advised to maintain their normal lifestyle during the study (e.g. dietary intake, exercise levels and non-smoking habits). It is especially important that participants do not experience substantial shifts in body weight/body composition during the study, as fluctuations can affect the observation relative to berry component utilization by the human body. If still interested in participating in the study, you will be asked to sign the study consent form. After signing the consent form, your inclusion/exclusion will be verified via confirmation of your BMI, measurement of resting blood pressure, and via a medical history and medication use questionnaire.

2. In the clinical screening visit (1 hour) at the Human Research Core (North Carolina Research Campus, 500 Laureate Way; Kannapolis, NC 28081), you will arrive fasted for 10 hours, and your BMI, measurement of resting blood pressure, medical history and medication use questionnaire will be assessed. You will also be asked to provide a midstream urine sample to establish kidney, liver and urinary tract health via a dipstick test (Urispec 11 way) for content of blood erythrocytes, urobilinogen, bilirubin, protein, nitrate, ketones, ascorbic acid, glucose, pH, specific gravity, and leukocytes. Female participants will also be assessed for pregnancy. After confirmation of eligible BMI, you will provide a fasting blood sample (approximately 0.29 oz. or ½ tablespoon) through venipuncture and used to establish health status via a comprehensive metabolic panel test to assess the blood content for glucose, calcium, albumin, total protein, sodium, potassium, carbon dioxide, chloride, blood urea nitrogen (BUN), creatinine, BUN/Creatinine ratio, total globulin, albumin/globulin ratio, alkaline phosphatase, alanine aminotransferase (SGPT), aspartate aminotransferase (SGOT) and total bilirubin. The results of the urine and blood analyses will be available in approximately 24-48h, when the participants will be notified about their eligibility and scheduled for the berry feeding visits.

3. You will have one week washout before your berry or berry product feeding visits, when you will be asked to consume a diet low in berries and red or purple fruits and vegetables as directed by the dietary exclusion list (Annex 2- "Food Exclusion and Alternatives List") provided. We will ask you record your diet (Annex 3- "Food Intake Record"), and collect 24h-urine during the two days preceding each berry feeding visit (Annex 4- "Urine Collection Instructions"). The study days will occur during weekdays. At the study day 1 (approximately 9.5-hour long) in the clinic, you will arrive fasted for 10 hours (having consumed only water), the clinical team will take receipt of previously collected urine (two 24-hour collections, one from each of the two previous days) and the food intake record from the two preceding days. Also, you will complete a basic medications assessment/questionnaire to establish fitness to proceed (e.g. to assess if you have fasted correctly and are free from symptoms indicative of compromised health), and record any medications being used onto the medical questionnaire. Your resting blood pressure, height, and weight will be measured. Additionally, urine (0-9h, 9-24h and 24-48h) and blood samples (at 0, 1, 3, 6, 9, 24 and 48 h) will be collected across the three study days for each berry or berry product

feeding visit. Failure to comply with fasting or dietary restrictions at first visit will require a further one week washout period; repeated failure to follow the fasting or dietary guidance during the study may result in withdrawal from the trial. This procedure will be repeated across 3 other study periods (for a totoal of 4 study periods). In the first feeding visit, you will receive either, in randomized order, one serving (approximately 5.3 oz) of two different commercially available blueberry varieties, a protein bar enriched with the equivalent of one serving of blueberries or a nutrient-matched control beverage. You will consume a dairy product, specifically whey protein beverage together with the berries in order to provide equivalent macronutrient contents across the feeding products. After the berry or berry product is given on day 1 of each feeding visit, breakfast will be provided, as well as lunch, dinner and snacks. Blood pressure, height, and weight measurements, and potential medication change record will be done on days 2 and 3 of after each berry feeding visit. Days 2 and 3 last about 1 hour. You will be provided with standardized berry-free meals and water during the visit days 1 and 2, and breakfast after blood collection on day 3. You will be asked to write your food and drink intakes during visit days 1 and 2, and to repeat these intakes on the following three feeding visits.

You will be asked to choose your standardized berry-free meals from a list of foods provided (breakfast, lunch, dinner and snacks) based on the following foods: white bread*/ bagel*/white roll* with cheese, cream cheese, honey, butter, salad dressing, ham, turkey, chicken, and or roast beef, chickpeas, plain breakfast biscuit, hard boiled eggs, chips, white rice, macaroni and cheese, noodles, cucumber, baby carrots, peas, canned or dried pineapple, canned or dried peaches, crackers (no wholemeal, dark chocolate, red fruits), butter cookies; and beverages: water (mineral, flavored or sparkling), milk (1% or 2% reduced fat, skim, lactose-free, or rice milk), diet soda, artificial fruit drink. During your full day visit to the clinic and the following day you will be asked to abstain from consuming coffee or tea which may result in the development of a headache which can be caused from caffeine withdrawal. Caffeinated diet beverages will be provided should you wish to consume them as an alternative to coffee or tea.
*Available as plain or gluten-free

The protein bars contain 27.5 g protein, dried blueberry (equivalent to 1 serving of blueberries), 20 g fat, 41.25 g carbohydrates, and 440 total calories /113 g. The protein bars do not contain any peanuts, soybeans or soy, eggs, fish, crustaceans, tree nuts, wheat, gluten, or sulfites.

4. Between the feeding visits, you will receive a “thank you” email about your participation and a reminder that you can observe approximately 2 weeks (11 to 20 days depending on scheduling constraints) of free-living compliance break, when you can return to your normal dietary habits and take a break from the study regime. This will be followed again by seven days of wash-out, urine collection and record of your food intake for two days before the next feeding visit day. This will be repeated for the remaining three berry or berry product feeding visits.

You will need to come to the Human Research Core on the North Carolina Research Campus, in Kannapolis on 14 separate occasions over a period of 3 months (total of 54.5 hours commitment). The blueberries or blueberry product will be consumed on 4 different feeding days, each followed by 2 follow-up visits. This equates to 4 feeding days (across the 4 study periods) and 8 one-hour visits. Before you are enrolled in the study you will also be required to come to the research campus for a ½-hour initial presentation and one 1-hour screening visit. For the 4 blueberry product feeding days, you will be with us for approximately 9 and 1/2 hours, while the following two visits will be less than 1 hour. The 4 separate feeding days will be spaced out over 11 weeks with about 2 weeks break between each of the feeding days.

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Appendix C: Description of IV Cannulas vs. Venous Blood draws at each time point

On the first day of each arm of the BAM study you will have 5 blood draws over a 9.5 hour period. The Human Research Core trained team will make every effort to ensure that this process is done with your safety and comfort as our top priority.

You will have the following options:

1. **Individual venous blood draws**. Blood from all five time points drawn from the most easily accessible, superficial veins in your forearms. We will make every effort to draw these samples from different sites in your arms if possible. Not everyone has accessible veins in both arms. If this is the case, all 5 samples may need to be drawn from one arm. We will, however, try to use the 2 different veins in your one accessible arm.

Note: There is the chance that we will have to try to find an accessible vein two times by one phlebotomist with 1 further attempt by a second phlebotomist if the first is unsuccessful.

2. **IV Cannula Placement.** You also have the option of having an IV cannula inserted into the vein in your arm at the beginning of the first day of each study period, or at any time during this day, except right before the last blood draw of the day. It will allow us to get the blood samples from the cannula, and minimize the inconvenience of sticking you multiple times. This is the same procedure that you have when you have an IV placed in your arm for hospital procedures. We will place a short, plastic cannula into the vein in your arm. This is done with a small needle covering the cannula that we place into the selected vein in your arm. We then remove the needle, leaving the plastic cannula in place. We will draw the blood that we need for your first time point out of the cannula, then we will flush the cannula with a small amount of sterile saline. Next, we will cap the cannula so that it is kept sterile and will not leak before your next time point. You will need to keep your arm as straight as possible in between time points to ensure the cannula stays in place. You must return to the lab every hour to have the cannula flushed. The cannula should be accessed by lab or study personnel only. If the cannula becomes dislodged at any time throughout the day, you should return to the lab immediately. You cannot leave the NRI building, where the phlebotomy laboratory is located, while the cannula is in your arm.

Note: There is a chance that the cannula cannot be used for all blood draws over the 9.5-hour period, as the cannula may get clogged or move out of place. If this happens, we must remove the cannula and perform individual blood draws for each remaining time point. We will make every effort to avoid this, but it does happen sometimes.

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Appendix D: Required Documentation to Process Travel Reimbursements for foreign nationals

Collecting the documentation listed below ensures that NC State is processing payments to international visitors in valid immigration status, and in the assessment of possible tax liability based on the visitor's tax status.

Documentation is a requirement even if the payment falls under the Accountable Plan.

F-1 students, H-1B, and TN Visa holders can not be paid honoraria.

J-1 Visa

- Copy of passport photo page
- Copy of J-1 visa in passport
- Copy of entry stamp in passport
- Copy of I-94 (Can be printed from: https://i94.cbp.dhs.gov/I94/#/home)
- Copy of DS-2019
- Letter of payment authorization from the sponsoring institution's Office of International Services, if the visitor's J-1 visa is not sponsored by NCSU
- Original signed W-8BEN

B-1 visa

- Copy of passport photo page
- Copy of B-1 visa in passport
- Copy of entry stamp in passport
- Copy of I-94 (Can be printed from: https://i94.cbp.dhs.gov/I94/#/home)
- Original signed W-8BEN

Visa Waiver Business (VWB) (ESTA)

- Copy of passport photo page
- Copy of entry stamp in passport
- Copy of I-94 (Can be printed from: https://i94.cbp.dhs.gov/I94/#/home)
- Original signed W-8BEN

**** ICT requires the original signed W-8BEN/W-9 and the original copies of collected immigration documents. Please send them to us via campus mail to Campus Box 7233 ****
(Failure to comply mail result in the delay of payment)

Thank you!