Institutional Review Board
Sarah J. Schlesinger, MD Chair
Dale Miller, BA CIP
Sr. IRB Specialist (212) 327-8411
Vanessa Smith, MPS, CIP, CIM
Sr. IRB Specialist (212) 327-8410
Hospital Bldg., Rm 201 Box 331

April 15, 2024

Paul Cohen, MD, PhD
RUH - Laboratory of Molecular Metabolism (Paul Cohen)
The Rockefeller University

RE:PCO-1051 Identification of thermogenic silencing regulatory factors as biomarkers of metabolic health in humans

Dear Dr. Cohen,

Thank you for submitting the modifications to documents for the above protocol (iRIS submission # 375150), as requested in our letter of February 1, 2024. On behalf of the Board, I have reviewed and approved the modifications.

Having met all of the criteria for approval outlined in 45 CFR 46.111 and 21 CFR 56.111, this study was reviewed and granted stipulated approval at the convened meeting of the Institutional Review Board (IRB) on **February 1, 2024**. The final approval period is **April 15, 2024 through April 14, 2025.**

The following documents were reviewed:

Type	Document Name	Version	Date Submitted into Workflow
Submission Response by Board:			
Institutional Review Board	Review Response Submission Form	Version 1.0	04/15/2024 02:49 PM EDT
	Review Response Submission Form	Version 1.0	
Submission Form:			
Submission Form	Initial Review Submission Form	Version 1.1	04/15/2024 02:49 PM EDT
Submission Form	Initial Review Submission Form	Version 1.0	
Submission Attachments:			
Application	Study Application	Version 1.1	04/15/2024 02:49 PM EDT
Application	Study Application	Version 1.0	01/23/2024 03:39 PM EST
Consent (English)	Barrow/Cohen ICF 11April2024	Version 1.2	04/15/2024 02:49 PM EDT
Consent	Barrow/Cohen ICF 1/24	Version 1.0	01/23/2024 03:39 PM EST
Document - Text for Advertisements	Advertisement Flyer Polar Bear	Version 1.0	04/15/2024 02:49 PM EDT

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Type	Document Name	Version	Date Submitted into Workflow
Document - Text for Advertisements	Advertisement Flyer Hands	Version 1.0	04/15/2024 02:49 PM EDT
Document - CCTS Utilization Report	CCTS Utilization Report	Version 1.0	04/15/2024 02:49 PM EDT
Document - Study Questionnaire	IPAQ Phone Questionnaire	Version 1.0	04/15/2024 02:49 PM EDT
Document - Study Questionnaire	DHQ3 Serving Size Questionnaire	Version 1.0	04/15/2024 02:49 PM EDT
Document - Schedule of Events	SOE 1/2024	Version 1.0	01/23/2024 03:39 PM EST
Document - Other Supporting Documentation	IRB Infographics	Version 1.0	01/23/2024 03:39 PM EST
Document - Other Supporting Documentation	Prescreening Survey	Version 1.0	01/23/2024 03:39 PM EST
Document - Other Supporting Documentation	Punch Biopsy SOP	Version 1.0	01/23/2024 03:39 PM EST
Document - CCTS Utilization Report	CCTS Utilization Report 10April2024	Version 1.1	04/15/2024 02:49 PM EDT
Document - CCTS Utilization Report	CCTS Utilization Report 1/24	Version 1.0	01/23/2024 03:39 PM EST
Document - Text for Advertisements	Advertisement Flyer	Version 1.1	04/15/2024 02:49 PM EDT
Document - Text for Advertisements	Advertisement Flyer	Version 1.0	01/23/2024 03:39 PM EST
Document - HIPAA Authorization form	HIPAA Form	Version 1.1	04/15/2024 02:49 PM EDT
Document - HIPAA Authorization form	HIPAA Form	Version 1.0	01/23/2024 03:39 PM EST

The number assigned to this protocol is **PCO-1051.**

Please note that submission for Continuing Review of this protocol is due no later than 9:30 am on **February 25, 2025.**

It is the Principal Investigator's responsibility, as required by Federal regulations, to (1) Submit any proposed changes in approved studies to the IRB for review and approval prior to initiation, except where necessary to eliminate apparent immediate hazards to the subjects; (2) To promptly inform the IRB, appropriate institutional officials, the Office for Human Research Protections (OHRP) and the FDA, if applicable of any unanticipated problems involving risks to subjects or others and research related injuries; (3) To obtain the informed consent of the participant in the manner and format approved; and (4) To resubmit to the IRB for continuing review at the interval determined by the IRB to be appropriate to the risk, but not less than once a year.

Sincerely yours,

Institutional Review Board
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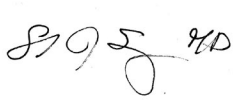

Signature applied by Sarah J Schlesinger on 04/15/2024 06:45:38 PM EDT

Sarah J. Schlesinger, MD
Chair, Institutional Review Board
The Rockefeller University
Federal Wide Assurance # 000004658

1.2)

1.0 General Information

***Please enter the full title of your study::**

Identification of thermogenic silencing regulatory factors as biomarkers of metabolic health in humans

***Please enter the study short title:**

Thermogenic Silencer Regulatory Factors in Humans
* This field allows you to enter an abbreviated version of the Study Title to quickly identify this study.

Is this Study using Subject Management?

○ Yes ◉ No

2.0 Add departments

2.1 List departments associated with this study:

Is Primary?	Department Name
○	**RUH** - Clinical Research Support Office (CRSO)
◉	**RUH** - Laboratory of Molecular Metabolism (Paul Cohen)
○	**RUH** - Rockefeller University Hospital (RUH)

3.0 Assign key study personnel(KSP) access to the study

3.1 * Please add a Principal Investigator for the study:

Name	Role	Training Record
Cohen, Paul, MD, PhD	**Principal Investigator**	View Training Record

3.2 If applicable, please select the Research Staff personnel:

A) Additional Investigators

Name	Role	Training Record
Barrow, Joeva, PhD	**Clinical- Co-Investigator**	View Training Record
Gomez Banoy, Nicolas, MD	**Clinical- Co-Investigator**	View Training Record
Walker, Jeanne Marie, DNP, ANP-BC	**Clinical- Co-Investigator**	View Training Record

B) Research Support Staff

Name	Role	Training Record
Li, Muying, MS	**Research Assistant**	View Training Record
Rauso, Anna, BS	**Facilitator**	View Training Record
Ronning, Andrea, M.A.	**Bionutritionist**	View Training Record

3.3 *Please add a Study Contact:

Name	Role	Training Record
Barrow, Joeva, PhD	**Study Contact**	View Training Record
Cohen, Paul, MD, PhD	**Study Contact**	View Training Record
Li, Muying, MS	**Study Contact**	View Training Record
Rauso, Anna, BS	**Study Contact**	View Training Record

3.0 Assign key study personnel(KSP) access to the study

Walker, Jeanne Marie, DNP, ANP-BC	**Study Contact**	**View Training Record**

The Study Contact(s) will receive all important system notifications along with the Principal Investigator. (e.g. The project contact(s) are typically either the Study Coordinator or the Principal Investigator themselves).

4.0 Rockefeller University Conflict of Interest

4.1 **Investigator Financial Conflict of Interest** **All KSP must complete an annual certification of their Significant Financial Interest ("SFI") disclosures in the University's online Research Administration System at https://RAS.rockefeller.edu. Disclosures also must be updated in connection with new human subjects research protocols ("Research Certification"), and within 30 days of discovering or acquiring a new SFI. To avoid delays in the IRB review process, when prompted by an email from rascoi@rockefeller.edu requesting an updated Research Certification, KSP should click on the Research Certification link contained in that email notification, or go to https://RAS.rockefeller.edu, to (a) review and update his or her SFI disclosures or certify that he/she has no updates, as appropriate, and (b) indicate whether any of his/her SFI disclosures are reasonably related to the design, conduct, or reporting of the research protocol. If a KSP discloses a SFI that might constitute a conflict of interest with respect to the proposed protocol, he or she must e-mail a copy of the Lay Summary of the draft protocol to Teresa Solomon, Esq. (solomot@rockefeller.edu). Doing so will facilitate addressing COI issues in step with the development of the study protocol. Non-compliance or tardiness in making or updating COI disclosures will result in a delay in IRB review.** **Institutional Conflict of Interest:**

As early as possible the PI (or a designee) preparing a clinical research protocol must review a list of entities in which The Rockefeller University has an Institutional Financial Interest at https://icoi.rockefeller.edu/account/login.php. If the proposed study involves any entity on that list, the PI (or designee) must notify Teresa Solomon, staff to the FCOI Committee, by e-mail solomot@rockefeller.edu and Sarah Schlesinger, Chair of the IRB, by email: schless@rockefeller.edu, provide the name(s) of the entities and a copy of the Lay Summary. Doing so will facilitate addressing institutional COI issues in step with the development of the study protocol. Failure to take steps to review and address potential institutional conflicts of interest will delay the IRB review process.

5.0 External Personnel

5.1 List external personnel who will be working on the study:

Name	Institution	Telephone	E-mail	Role
Joeva Barrow	Cornell University	352-575-7051	jbarrow@rockefeller.edu	Clinical- Co-Investigator
Muying Li	Cornell University	917-593-9655	MLi02@rockefeller.edu	Research Assistant

6.0 Delegation of Authority

6.1 Enter authorized activities for all Rockefeller University personnel named on the study.

Activity Codes:

1. Informed consent **
2. Inclusion / exclusion criteria
3. Medical/medication history *
4. Perform Physical Exam *

4a. Write / Sign LIP orders *

5. Skin assessments and photos
6. Study drug dispensing *
7. Study drug administration *
8. Study drug reconciliation
9. Study drug compliance
10. Administer study questionnaire(s)
11. Participant recruitment
12. Perform assays
13. Specimen / sample analysis
14. Lumbar puncture *
15. Femoral line placement *
16. Central line placement *
17. Insulin clamp procedure *
18. Leukapheresis *
19. Sigmoidoscopy *
20. Fat biopsy *
21. Skin biopsy *
22. Conduct sleep study
23. Diet design and preparation
24. Nutritional assessment and counseling
25. Addition of PABA to food
26. Data analysis
27. Data review
28. Data management
29. Maintain regulatory documents / files
30. Complete CRF's

Add up to three additional authorized activities specific to this study (do NOT add activities that have previously designated codes):

31:	Apply Cooling Vest
32:	Hip and Waist Measurement
33:	Punch Biopsy

Activity Codes Continued:

34. Behavioral Testing
35. Bod Pod
36. Bone Marrow Aspiration *
37. Neuropsychological Testing *
38. Conduct Focus Group
39. Conduct Smell Study
40. Genetic Counseling *
41. Apply EEG Electrodes **
42. Olfactometer Test
43. Study Participant Teaching
44. Resting Energy Expenditure

45. Source Document Review & Correction
46. Medical Photography
47. See 4a
48. Adverse Event Assessment
49. Clinical Trial Registration
50. Study Support Drug Dispensary
51. Internal Monitoring
52. Randomization

Enter delegation of authority for Rockefeller University Key Study Personnel:

NOTE:

* Indicates procedures requiring the individual complete specific credentialing **BEFORE** the activity may be added to their delegated activities.
** Indicates procedures requiring the individual complete specific training **BEFORE** the activity may be added to their delegated activities.

Name	Title	Authorized Activities	Start Date	End Date
Cohen, Paul, MD, PhD	PI	4a,26,27,51	01/12/2024	
Barrow, Joeva, PhD	Co-I	1,2,10,13,26,27,28,30,31,45,49,51	01/12/2024	
Li, Muying, MS	Rsch Technician	1,2,10,13,26,27,28,29,30,31,45,48,51	01/12/2024	
Ronning, Andrea, M.A.	Bionutritionist	32,35	01/12/2024	
Walker, Jeanne Marie, DNP, ANP-BC	Co-I	1,2,3,4,4a,10,33,48	01/12/2024	
Rauso, Anna, BS	Facilitator	1,29	01/12/2024	

Enter delegation of authority for additional Rockefeller University Key Study Personnel:

Name	Title	Authorized Activities	Start Date	End Date
No results found				

Enter the authorized activities for External Personnel:

Name	Title	Authorized Activities	Start Date	End Date
No results found				

7.0 Study Description

7.1

Study Classification

Full Review

7.2

* Submission Request Category

Note: For each submission, please designate the level of review, or "Submission Request Category" you are requesting. When completing this field, please indicate the level of review you are requesting for the specific submission you are working on.
For example, if you are submitting an Expedited Amendment request to change the Key Study Personnel on your existing Full Board study, you should select "Expedited Review" in both the Amendment Submission Form and Study Application. The IRB will confirm an Expedited review of the Amendment submission is appropriate, and the overall study will remain classified as a full Board review. Please see the help bubble for guidance.

To submit a request for a Not Human Subjects research determination, please exit this form and select the "Not Human Subjects Research Determination" form under Create a New Study.

- ○ Exempt from Review
- ○ Exempt with Limited Review
- ○ Expedited Review
- ◉ Full Review

7.3 * **Lay Summary**

Please provide a summary of your study in lay language that is easily understood by a non-scientist. The summary should be no more than half a page (500 words or less) and should contain a clear statement of the rational for the study.

Please click on the help bubble to get the information on " How to use iRIS text editor."

Please provide a summary of your study in lay language. The summary should be no more than a half page (500 words or less) and should contain a clear statement of the rationale for the study.

A promising approach to correct the metabolic dysfunction associated with obesity is to activate brown fat non-shivering thermogenesis (NST). A critical limitation with NST as a therapeutic option, however, is that this beneficial process is silenced under human physiological temperature conditions and the mechanisms of how this occurs is unknown. This study will be the first to identify human NST silencing factors that may be targeted for the treatment of obesity and metabolic disorders.

7.4

* **Public Health Impact Statement**

Provide a brief plain language statement (100 words or less) of the value of the research proposed and its potential impact on population health. Additional instructions located in Help.

Why- Obesity and its associated health risks are the leading causes of preventable death worldwide. It may be possible to fight obesity by activating human brown fat- a type of fat associated with heath --but the tissue is silenced (not metabolically active) for most of human life. Cold exposure can turn on brown fat, but the mechanisms controlling its silencing are unknown.

What- We will define the factors that control whether brown fat is active or silenced by studying the proteins and other chemicals released into the blood of volunteers subjected to the kind of cold-exposure that stimulates brown fat.

How- Understanding how to control the activation of healthy brown fat could provide insights into the design of new therapeutic approaches to combat or prevent obesity and type 2 diabetes.

8.0 Clinical Trial Registration

8.1

Clinical Trial Registration

The types of studies listed below must be registered at **Clinical Trials website** before enrolling the first participant in order to be in compliance with federal regulations and preserve the opportunity to publish the study in journals that adhere to the **ICMJE guidelines**. Please check the answer that best applies.

- ○ Study involves testing of FDA regulated drugs or biologics (See HELP)
- ○ Study is funded by the NIH, and meets the definition of a "clinical trial" (see HELP)
- ○ Study meets the ICMJE definition of a "clinical trial" (See HELP)
- ○ Additional funding agency or journal requires clinical trial registration
- ◉ None of the above

If you selected 1, 2, 3, or 4 you must register your trial with ClinicalTrials.gov through the Rockefeller University institutional account. Please contact the Clinical Research Support Office x7408 for assistance.

9.0 Study Overview/Summary

9.1 * Who initiated this study?

Please specify one:

- (•) Principal Investigator Initiated
- ( ) Industry Initiated
- ( ) Other

9.2 *Are other institutions involved in the study?

- ( ) No
- (•) Yes

Please enter the name and IRB approval details for each involved institution. Include a description of each site's involvement in the Methods and Procedures section.
Attach external IRB approval letters in Other Study Documents.

	Name of Other Institution	Date of IRB Approval by Other Institution	Date of Pending Approval by Other Institution	Date of IRB Expiration at Other Institution	Date of Exemption at Other Institution	Check if Other Institution is relying site in a Single IRB arrangement
	Cornell University		06/03/2024			☐

9.3 * Is this a multi-site trial using a single IRB (sIRB) review arrangement? Please see help bubble for definition.

( ) Yes (•) No

9.4 * Who (What) is to be studied?

- [x] Human Subjects - including coded samples and/or data with links to Identifiers
- [ ] Deidentified Samples - unable to be linked to identifiers by receiver
- [ ] Data Only - unable to be linked to identifiers
- [ ] Identifiable samples or data for exemptions (per 104 (s)(4))

9.5 *Study Type:

- (•) Interventional
- ( ) Observational

9.6 The initial date of IRB approval/determination was:

04/15/2024

9.7 * What is the expected duration of the study?

Two years

9.8 * Are any of the following agents to be used in the study?

Check all that apply:

- [ ] FDA Approved Drug
- [ ] FDA Approved Drug for Off-Label Purpose (This might require an IND)
- [ ] Investigational New Drug
- [ ] Biologic Agents
- [ ] Nutritional Supplements
- [ ] Placebo
- [ ] Vaccines
- [x] No Agents
- [ ] FDA Exemption to use Study Drug

9.9 * Are investigational devices to be used in the study?

( ) Yes (•) No

9.15 Special Research Procedures

Does the study propose to directly involve participants in the following special research procedures?

- ☐ Recombinant DNA
- ☐ Gene Therapy
- ☐ Fetal Tissue
- ☐ Embryonic Stem Cells
- ☐ Induced Pluripotent Stem Cells
- ☐ CRISPR-Cas9

If any item is checked, please see Help for details.

9.16 * Radioactive Isotopes Involved

Will participants be exposed to any radiation other than routine x-rays solely for clinical care purposes?

- ○ Yes ◉ No

10.0 Interventional

10.1 *Interventional, please specify:

- ◉ Open Label
- ○ Single Blind
- ○ Double Blind
- ○ Other

11.0 Study Phase:

11.1 Study Phase:

Select where applicable

- ○ Phase 0
- ○ Phase I
- ○ Phase I/II
- ○ Phase II
- ○ Phase III
- ○ Phase IA
- ○ Phase IB
- ○ Phase IIA
- ○ Phase IIB
- ○ Phase IB/IIA
- ○ Phase IIB/IIIA
- ○ Phase IIIA
- ○ Phase IIIB
- ◉ N/A

12.0 Objectives and Rationale

12.1 * Overview

Briefly state the ***purpose of this study***. Give enough background and rationale to provide both scientists and lay members of the IRB and ACCTS with the basis for exposing human participants to the risks involved.

Obesity and associated metabolic disease such as type 2 diabetes continue to be one of the leading causes of death worldwide, demanding additional research into novel treatments beyond our current options. One promising experimental approach to overcome the metabolic dysfunctions associated with obesity, such as insulin resistance and glucose imbalance, is to activate brown fat non-shivering thermogenesis (NST). Activated human brown fat increases energy expenditure at a molecular level and is associated with both improved insulin tolerance and glucose homeostasis. *A critical limitation with human brown fat as a therapeutic option, however, is that its beneficial metabolic potential is restricted in a silenced state under physiological temperature conditions for most of human life. The regulatory factors that govern this silencing process are completely unknown*. While many groups continue to seek novel mechanisms to activate brown fat, we present a unique approach, aiming to decipher the mechanisms that govern human brown fat silencing. We hypothesize that if we can define the regulatory factors that silence brown fat NST, then these factors can be targeted for ablation to eliminate the "off switch", thereby keeping brown fat in a constitutively active state. Identification of human NST silencing factors will be critical to unlock the metabolic benefits of human brown fat and would represent promising treatment opportunities for type 2 diabetes and other obesity-related disorders. We have identified a suite of silencing factors in mice and given our strong proof-of-concept studies, we anticipate that the BAT silencing regulatory program will also play a critical role in humans. We also anticipate that these BAT silencing regulatory factors will be differentially expressed both in lean vs obese individuals and between individuals with

and without type 2 diabetes. Understanding these relationships will allow for precision treatment opportunities for type 2 diabetes in the future.

The overall goal of this proposal is to unlock the metabolic benefits of human brown fat by defining the regulatory mechanisms that keeps BAT in a silenced state. We will generate the first human secretome and transcriptome compendium from human plasma and subcutaneous adipose tissue respectively which will be composed of target proteins, metabolites, and genes that are differentially expressed in response to NST silencing conditions. Top candidates from our profiling will then be functionally validated in human adipocytes for their role in NST silencing. Our work will be an important resource for the field and will identify novel candidates that may harbor regulatory potential to govern the NST silencing process in humans. These factors can then be targeted to promote the constitutive activation of NST in order to overcome the metabolic dysfunction associated with obesity and metabolic disease. Given the invasive nature of direct human brown fat sampling, we will instead interrogate circulating factors in human plasma as a proxy for metabolic health. Indeed, many groups such as Bruce Spiegelman, Camilla Scheele, and many others have reported secreted circulating factors derived from human brown fat termed "BATokines". We hypothesize that if these circulating factors are present in the NST active stage, then NST silencing factors may also be present in circulation during the silenced state. In addition, we will also obtain subcutaneous adipose tissue for RNA profiling to identify genes that are upregulated under NST silenced conditions compared to cold exposure.

12.4 * Engaging Stakeholders: Describe any plans to engage other stakeholders (Scientists, practitioners, patients, advocacy groups, etc.) for hypothesis generation, or feasibility purposes.

Input for this study was obtained from Dr. Carol Haft, PhD. who is a program director in the Division of Diabetes, Endocrinology, and Metabolic Diseases (NIDDK) at the NIH.

12.5 * Hypothesis

Describe the ***research hypothesis*** in a single sentence.

We hypothesize that the NST silencing regulatory factors that we identified in mice, also exist in humans and are differentially expressed in lean vs obese human subjects and in individuals with and without Type 2 diabetes.

12.6 * Aim(s)

Indicate how you will ***address the hypothesis*** (e.g., to compare groups, to estimate a parameter, to ascertain feasibility). Since the sample size determination is usually based on the primary aim only, the primary aim should be sufficient to justify the study.

Aim 1. Define the human secretome under NST silencing conditions, in lean and obese health volunteers, and individuals with type II diabetes, who are undergoing controlled cold-exposure and rewarming to induce and resilience brown adipose tissue activation.

Aim 2. Define the human adipose tissue transcriptome in response to NST silencing conditions to identify novel genes that can be targeted for the treatment of obesity and metabolic disorders.

12.7 * Primary Outcome(s)

Indicate which ***variable(s)*** will be assessed to judge the primary specific aim. Give measurement units, if applicable.

Generation of transcriptomic, proteomic, and metabolomic datasets of human candidate genes, proteins, and metabolites.

12.8 * Secondary Outcome(s)

Indicate which ***additional variable(s)*** will be assessed to judge the secondary outcome(s). Give measurement units, if applicable.

Nutritional and anthropometric assessments of individuals correlated to expression patterns of human NST silencer regulatory factors.

Association of individual nutritional and anthropometric assessments to expression pattenrs of Human NST silencer regulatory factors.

12.9 * Methods and Procedures

Please provide a description of the laboratory and clinical analyses and procedures that will be performed. Include the role of external collaborators and consultants when appropriate. Please refer to Help text for Guidance.

Remote Pre-Visit and Consenting

1. The recruitment team at the Rockefeller University (RU) will recruit individuals from the RU Research Participant Repository (RKO-0648) who meet the eligibility criteria for the study (age, BMI). The recruitment team will direct participants to complete an electronic pre-screening survey through REDCap to further gauge eligibility criteria (i.e diabetes status and management).

2. The recruitment team will then refer eligible participants who have passed the pre-screening metric to the Barrow-Cohen research team who will then provide participants with the informed consent document via email through REDCap according to RU Telephone/eConsent SOP for review.

3. The Barrow-Cohen research team will then schedule a Zoom conversation to review a 1-page infographic containing the study design and researchers will answer any questions participants may have. After the protocol is fully described, if the individual wants to enroll, they will be guided through eConsent process by the Barrow-Cohen research team. Participants will be asked to provide consent by signing the eConsent via REDCap

according to the established RU eConsent SOP and will be enrolled in the study. A suitable date for in-person on-site Visit #1 will be established at the end of the Zoom meeting.

Requirements prior to VIST #1.

All subjects will be required to fast overnight for 12 hrs prior to the site visit (21:00 – 09:00, study will commence at 09:00 +/- 1 hour) and refrain from caffeine and excessive exercise (i.e. vigorous aerobic exercise, such as running or gym workout sufficient to increase the heart rate and perspiration) for 12 hours prior to the visit.

VISIT #1 (On-Site)

This meeting will take place at the Rockefeller University Hospital and will take approximately 2-3 hours. During this meeting, we will

- Obtain anthropometrics measurements in a metric system from the participants including the weight and height to calculate Body Mass Index (BMI).
- Body fat and muscle composition will also be assessed via Bod Pod following Rockefeller's standard operating procedures.
- Clinical staff will then obtain blood (35mL) for basic clinical labs (glucose, A1C, TSH, T3, T4 etc).
- Female subjects will complete a point-of-care urine pregnancy and will be asked to provide information about their menstrual cycle.

Following these assessments,

- A breakfast meal prepared by the Rockefeller Bionutrition metabolic kitchen will be provided to the participants.
- Participants will then engage in comprehensive nutrition and anthropometric assessments. Participants will first fill out the Diet History Questionnaire III (DHQ III) by the National Cancer Institute online (**https://epi.grants.cancer.gov/dhq3**) to obtain diet quality and patterns information under the supervision of research staff.
- Research staff will then conduct a structured interview of the International Physical Activity Questionnaire (IPAQ) to evaluate participant's physical activity level.
- Following the nutrition assessments, the Barrow research group will calculate estimated energy requirements (EER) and nutrition requirements using the gold standard EER equations developed by the National Academies of Sciences, Engineering, and Medicine *Dietary Reference Intakes for Energy (DRI) 2023* for individuals.

The Barrow research team will then formulate an individualized tailored nutrition beverage that will meet 33% of each participants' daily EER. This nutrition beverage (Katefarm Nutrition Shake which is USDA Organic, Non-GMO, plant-based, vegan, and does not contain milk, eggs, fish, shellfish, tree nuts, peanuts, wheat, or soybeans **https://shop.katefarms.com/products/nutrition-shake**) will be provided to participants on Visit #2 to ensure that study participants are maintained at nutrient baseline and maintained in a fed state throughout the study. The formula will be provided to Rockefeller Bionutrition department, by the Barrow research team, for storage, preparation and administration. A suitable date for Visit #2 (experiment date) will be established at the end of Visit 1.

Requirements Prior to VISIT #2

All subjects will be required to have a hearty meal of choice the night before the visit and fast overnight for 12 hrs prior to the visit (21:00 – 09:00, study to begin at 09:00 +/- 1 hour) and refrain from caffeine and excessive exercise (i.e. vigorous aerobic exercise, such as running or gym workout sufficient to increase the heart rate and perspiration) for 12 hours prior to the visit.

NOTE: Based on data from laboratory animals, exercise is linked with brown fat activation, thus refraining from exercise immediately prior to the experiment will minimize potential variability in BAT activation between all participants.

VISIT #2 (On-Site)

Participants will engage in a 6.5-hour study that will encompass a customized cold environmental exposure, and subsequently a thermoneutral exposure period. The time length for cold and rewarming periods were selected based on previous research by Aaron Cypess and others in the field. There will be five blood collections of 16mL each for a total of 80mL over a span of 6.5 hours and two punch biopsies obtained after cold and warm environmental exposure that will be cryopreserved for transcriptomic analysis. The total volume of blood sampling (80 mL) is in accordance with the American Red Cross safety guidelines.

Baseline (30min). Participants will arrive to the Rockefeller University Hospital at 9am and enter a patient room kept at room temperature conditions (25^{o}C). They will be instructed to de-robe in private quarters and don hospital gowns and the first of five blood draws of 16mL will be collected into both EDTA-treated and non-treated tubes (8mL each) and stored at 4^{o}C for later plasma and serum processing respectfully for proteomic and metabolomics analysis. After this, the Bionutrition department will measure the individualized tailored chilled complete liquid nutrition meal replacement beverage (Katefarms Nutrition Beverage) at the amount provided by the Barrow research team to meet a third of participants' dietary reference intakes (DRI) for energy based on their individualized EER that was calculated in Visit #1. This formula will then be administered to each research participant. Bionutrition will mark the order as complete, in Cerner, once it is provided to the research participant. This will represent "breakfast" and ensure that all participants begin the cold exposure study at nutrient baseline to remove any confounding effects from diet or fasting. The second blood sampling will then

take place 30min following feeding. Throughout the study, participants will be regularly offered water to ensure that they are properly hydrated.

Cold Exposure (3 hours). Water-perfused cold vests (**https://www.polarproducts.com/polarshop/pc/CoolOR-13-Quart-System-with-Arctic-Chiller-p24757.htm**) will be placed over the hospital gowns on study participants. The cold vests are connected to an automated water-cooling artic chiller reservoir that delivers continual cool water infusions to the vest to maintain a constant cold temperature. The Cohen lab has vests of varying sizes (S, M, L, XL, XXL) to comfortably fit all study participants. We will employ the established adaptive cooling method where the cooling temperature is set to 2^{o}C above an individual's shivering threshold. This will ensure that muscle thermogenesis is not being engaged to maximize the activation of brown fat non-shivering thermogenesis. The starting infusion temperature will be set to 16^{o}C and the Barrow and Cohen research teams as well as the Rockefeller hospital staff will monitor for signs of shivering using a combination of direct observation and participant reporting. When shivering occurs, the temperature setpoint on the cold vest will be raised by increments of 2^{o}C until shivering subsides which will be the defined cooling temperature for that individual throughout the study period. If shivering does not occur withing a 10 min period, then the temperature will be lowered by increments of 2^{o}C until shivering begins, at which the setpoint will be increased by +2^{o}C. Participants will be cold exposed for a period of 3 hours as has previously been shown to induce rapid activation of BAT based on human fluorodeoxyglucose PET/CT scans. During this time, study participants will be comfortably seated or reclined and can engage in reading and/or digital entertainment. Rockefeller hospital staff will check on the participants every 30min and monitor for signs of discomfort and/or hypothermia. Following the 3-hour cold exposure period, the third blood draw sample will be collected as described above. The cold vests are safe for human use, and these are well established protocols that have been successfully performed by Dr. Cohen's IRB-approved studies and others in the metabolism field. These are also the official recommended experimental guidelines employed by the Brown Adipose Reporting Criteria in Imaging Studies (BARCIST) for humans.

Re-Warming (3 hours). Following cold exposure, the cold vests will be removed, and participants will be offered a warm blanket to ease the transition from cold back to warm temperatures. Participants will then be moved to an adjacent warm room maintained at 30^{o}C and asked to return to the resting position of their choice. Blood sampling will occur 45 min after the transition to warm temperatures as described above. This will be a critical sampling period as we hypothesize that the NST program will be shutting down in response to the warm temperatures and therefore will maximize the potential of identifying regulatory factors that govern the acute phase of NST silencing. Following blood collection, participants will be provided a second liquid nutrition meal replacement beverage meeting a third of their dietary reference intakes (DRI) for energy at ~1:15pm to represent the "lunch" meal. This will ensure that participants continue to remain in the fed state throughout the study. Participants will then engage in reading and/or digital entertainment for the remainder of the 3- hour warm exposure period. The last blood collection will take place as described above and we anticipate that these samples will reveal potential regulatory factors that govern the chronic phase of NST silencing.

Adipose Tissue Biopsy

At the end of both the cold and warm exposure periods, Jeanne Walker, DNP, ANP-BC at the Rockefeller University will perform a punch biopsy according to established standard operating procedures. Briefly, the punch biopsy is a minor surgical procedure where a small piece of skin and some underlying fat tissue is removed from the participants lower abdomen after it has been numbed with local anesthesia (1-2% xylocaine). One biopsy 6 mm in diameter (about ¼ inch, the size of a pencil eraser) will be obtained. The skin will be closed with 2 absorbable sutures. Punch samples will be transferred to 1.5 mL microcentrifuge tubes, flash frozen in liquid nitrogen, and stored in -80^{o}C. Samples will be transported back to the Cohen and Barrow laboratories on dry ice where they will be processed for downstream transcriptomic analyses.

Role of the Collaborator

Dr. Barrow will obtain approval from the Cornell Ithaca IRB for the specimen analysis taking place there. A copy of the Cornell RB approval letter will be submitted via an amendment prior to beginning work and any transfer of materials to that site.

Dr. Joeva Barrow PhD, RD. and her research technician Muying Li, MS. RD. (Cornell University, Ithaca, NY) will be directly involved in all phases of the study (nutrition assessment, cold and rewarming exposure, and adipose tissue biopsies). They will reside in NYC for the duration of the study and will be on site. Following completion of the study, half of all study samples (blood, adipose tissue etc) will be transported to Cornell University on dry ice for downstream proteomic, transcriptomic, and metabolomic analyses to identify regulatory factors that are critical for NST silencing and therefore harbor the potential to combat obesity and metabolic disease. The Cohen laboratory will retain the other half of the samples for complementary rigorous analyses. The Barrow and Cohen laboratories will maintain regular communication and will each be listed as co-authors on publications in peer-reviewed journals that arise from each independent group.

12.10 * Data Analysis

Describe method(s) of data analysis.

Diet History Questionnaire III (DHQ III) web-based software is integrated with a DHQ III analysis program that automatically calculates nutrient and food group intakes and the Healthy Eating Index (HEI)-2015 based on

questionnaire responses and produces analysis files. Detailed data output of DHQ III can be found on its website: **https://epi.grants.cancer.gov/dhq3/data.html**.

The Barrow laboratory will use the "Guidelines for Data Processing and Analysis of the International Physical Activity Questionnaire (IPAQ)" as the scoring protocol to analyze data and calculate the Metabolic Equivalents (METs) values from the short IPAQ responses. The MET values will be converted to Physical Activity Level (PAL) according to Table 12-1 Intensity and Impact of Various Activities on Physical Activity Level in Adults from the National Academies of Sciences, Engineering, and Medicine *Dietary Reference Intakes for Energy (DRI) 2005.* PAL categories (PALCAT) will be used later for the Estimated Energy Requirements (EER) calculation. PALCAT includes sedentary (PAL ≥ 1.0 < 1.4), low active (PAL ≥ 1.4 < 1.6), active (PAL ≥ 1.6 < 1.9), and very active (PAL ≥ 1.9 < 2.5).

Body Mass Index (BMI) will be calculated using the metric system via the BMI Calculator from CDC. Link to the calculator: **https://www.cdc.gov/nccdphp/dnpao/growthcharts/training/bmiage/page5_1.html**.

The formulas to calculate EER is from the Table S-3 Summary Table of EER Equations Based on TEE Prediction by Age, Sex, and Physical Activity: Adults, National Academies of Sciences, Engineering, and Medicine *Dietary Reference Intakes for Energy (DRI) 2023.*

Whole blood stored at 4^{o}C from our five collection points will be processed within 24 hours of collection to extract plasma for proteomic and metabolomics analysis. Briefly, blood samples stored in EDTA-coated tubes will be centrifuged for 10min at 4^{o}C for 2000 xg to pellet cells. Plasma will be retained and aliquoted into sterile 2 mL microcentrifuge tubes, flash frozen and stored at -80^{o}C for transport to the Barrow and Cohen laboratories. In regard to the blood samples collected in the non-EDTA tubes, they will be placed at room temperature for 20-30min to promote clotting, then blood samples will be spun down at max speed and the serum fraction will be retained and aliquoted into 2mL microcentrifuge tubes and stored at -80^{o}C transport to the Barrow and Cohen laboratories.

8.8 STATISTICAL MEASURES

All statistics will be performed with the consultation of both the Cornell and Rockefeller University Statistical Consulting Units that employs dedicated statisticians to assist with research studies. Briefly, human participant recruitment numbers were calculated based power analysis with an alpha value of 0.05 and an effect size of 10-20% to yield statistical significance based on previous human studies performed in the field. An n=20 per group for our proteomic, metabolomic, and transcriptomic analysis will produce high scientific rigor and reproducibility. Statistics for our proteomic analysis will utilize target peptide signals normalized by total peptide amount with P-values calculated by Student's T test with correction for multiple testing using the Proteome Discover 2.4 software. Metabolomics and transcriptomics statistical analyses will be performed by Student's T test according to core facility standards and will be confirmed using the GraphPad Prism 9 software.

12.11 * Explain the rationale for the choice of statistical measures and the number of participants proposed for the study, including the power calculations when applicable.

This is a pilot study that will provide data for power analysis in future studies. A biostatistician will be consulted to guide clinical data integration and correlations with blood biomarkers and genes discovered in this study.

12.12 * Will samples be coded?

(•) Yes ( ) No

If Yes, Please describe coding scheme consistent with GCP. If samples will not be coded, please provide justification for this proposed departure from GCP practice.

JBA-10 1A- Cooling
JBA-10 1B- Rewarming
There are 6 blood draws and 2 optional biopsies.

If available, upload the Data and Sample Sharing Management Plan approved by RU IT.

Version	Title	Category	Expiration Date	Document Outcome	View Document

No Document(s) have been attached to this form.

13.0 Participants of Study

13.1 Specify age range of participants:

* Minimum Age:

18

* Maximum Age:

35

Please note: If the age of participants indicated is less than 18 years old, you will be prompted to attach a Pediatric Assent form later on in the submission process. A link to the Pediatric Assent form can be found in the Help link to the right, or this form can be downloaded later on in the submission process.

13.2 * Indicate the gender(s) of the participants:

- [x] Female
- [x] Male
- [x] Unknown
- [ ] Not Reported

13.3 * Indicate projected enrollment by race and ethnicity. See Help for disease/volunteer population demographics.

Ethnic Category	Sex/Gender			
	Females	Males	Unknown or Not Reported	Total
Hispanic or Latino	18	16	0	34
Not Hispanic or Latino	46	40	0	86
Unknown (individuals not reporting ethnicity)	0	0	0	0
Ethnic Category: Total of All Subjects*	64	56	0	120
Racial Categories				
American Indian/Alaska Native	0	0	0	0
Asian	10	10	0	20
Native Hawaiian or Other Pacific Islander	0	0	0	0
Black or African American	17	16	0	33
White	31	29	0	60
More Than One Race	0	0	0	0
Unknown or Not Reported	6	1	0	7
Racial Categories: Total of All Subjects*	64	56	0	120

13.4 Exclusion of Protected Groups:

***Research involving human participants should be designed/conducted to be as broadly inclusive as possible regarding sex, gender, race, age, and ethnicity. Exclusions regarding these characteristics require an explanation of the rationale and justification.**

Will participants of a specific sex/gender/race/ethnicity/age or other protected group characteristic be excluded from participation?

- ( ) Yes
- (•) No

13.5 Vulnerable Populations

Indicate whether any of the following populations will be included in the study:

- [ ] Children
- [ ] Pregnant Women
- [ ] Cognitively Impaired Persons
- [x] RU Employees
- [x] RU Students
- [ ] Other:

If you checked any of the above, give a brief explanation of the need to use these particular individuals:

If the participant is a Rockefeller University employee, does she/he work within the Laboratory of the Principal Investigator or Co-Investigator(s)?

- ( ) Yes
- (•) No
- ( ) N/A

If the participant is a Rockefeller University student, does she/he work within the Laboratory of the Principal Investigator or Co-Investigator(s)?

- ○ Yes
- ◉ No
- ○ N/A

13.6 ***What is the total number of evaluable participants you plan to enroll at Rockefeller University Hospital over the course of the entire study?**

120

13.7 ***What is the total number of participants who will need to sign consent *at Rockefeller University Hospital over the course of the entire study* to result in the desired number of evaluable participants?**

140

13.8 ***What is the total number of participants you plan to sign consent *at Rockefeller University Hospital in the next year?***

60

13.9 ***What will be the total number of evaluable participants *at all sites over the course of the entire study?***

120

13.10 Inclusion Criteria

Please list participant inclusion criteria:

Order Number	Criteria
1	Age between 18 years old and 35
2	Lean group: BMI is between 18.5 and 24.9. A1C <5.7%
3	Obese group: BMI is ≥30, A1C <5.7%
4	Obese group with Type II diabetes: BMI is ≥30, A1C is >6.5% If on oral medication for diabetes management, A1C may be < 6.5% The following medications are also acceptable: statins, aspirin, ACEi, ARB.

13.11 Exclusion Criteria

Please list participant exclusion criteria:

Order Number	Criteria
1	Diabetes type I (self-report)
2	Diagnosis of thyroid disease (including goiter, hyperthyroidism, hypothyroidism, thyroiditis) (self-report)
3	Diagnosis with cancer including skin cancer (self-report)
4	Diagnosis or evidence of Raynaud's Syndrome or systemic sclerosis (self report)
5	A recent diagnosis of COVID-19 (last 2 weeks) or hospitalized at the time of diagnosis with COVID-19
6	Any vaccine administration within two weeks preceding the study procedure
7	Currently pregnant
8	Currently taking any prescribed medication other than oral contraceptives Treatments for weight loss or any other supplements that may alter weight or metabolism are not acceptable Vitamins are acceptable
9	Has consumed nicotine (smoking, inhaling, ingesting) within the last 6 months
10	Has used illicit drugs within the last 6 months (marijuana users are eligible unless consumed in the last 30 days).
11	Any medical, psychological, or social condition that, in opinion of principle investigators, would jeopardize the health or well-being of the participant during the study procedure or integrity of the data
12	Diabetes Type II that is managed by insulin.

13	Steroid use in the last 30 days to the exclusions

14.0 Schedule of Events/Study Plan

14.1

Instructions:New Studies:

- **A Schedule of Events is required for all new studies involving interactions with human subjects.**
- **The iRIS Study Plan will not be accepted for new protocols.**
- **A template Schedule of Events is available on the IRB Website. For any new study, populate the template with the visits and procedures for the study.**
- **The content of the Schedule of Events should be consistent with any descriptions of study procedures that may be in the protocol text and informed consent.**
- **Attach the completed Schedule of Events document to the Submission Form in the Schedule of Events section.**

Existing Studies: For existing studies, investigators may elect to update the existing Study Plan OR may replace the Study Plan with a Schedule of Events, following the instructions above for new studies.

Attach the Study Plan (an option only for studies with pre-existing Study Plans):

No Study Plan Templates have been associated.

*** What is the total number of outpatient visits for all participants projected for the next year?**

60

*** What is the average length of each outpatient visit (in hours)?**

3

*** What is the total number of Day Patient visits for all participants projected for the next year?**

60

*** What is the average length of each Day Patient visit (in hours)?**

7

*** What is the total number of inpatient days for all participants projected for the next year?**

0

15.0 Consent Procedure

15.1 * This study will use the following types of informed consent:

- [x] Informed Consent Form Standard - a standard consent form with instructions for adapting it to your study
- [ ] Consent Form Genetic- a consent form designed for a study where genetic testing (as defined by NYS law) is to be done in the CURRENT study
- [ ] Consent for studies including genome wide sequencing
- [ ] Pediatric Assent Form (To be used in addition to Consent) for Pediatric patients
- [ ] Other (e.g., waivers, electronic informed consent)

Links to the **Standard Consent, Genetic Testing Consent** and the **Pediatric Assent** forms can be found in the Help link to the right, or these forms can be downloaded later on in the submission process.

15.2 * Indicate the consent process to be used. (See Help for CCTS SOP)

Describe how the required information is being presented to participants (consent form, orally, information sheet, etc.). Attach a copy of what is being presented to participants (usually the ICF and Assent forms).

Prior to the initiation of any study related procedures, the potential subjects will be given a copy of the most recent IRB stamped and approved informed consent form to read. Additionally, the PI or study staff member who has been designated and is proficient in the consent form process will discuss the specifics of the study including but not limited to the purpose of the research, procedures, time commitment, required tasks, test article or device, alternative treatments, benefits, risks, confidentiality etc. in a comprehensible (non-scientific) manner, using language readily understandable by the subject. Subjects will be told that participation is voluntary and that, if they do not give informed consent, they will not be penalized. The person obtaining informed consent will assure the voluntariness of the subject. THe Zoom consent process will be obtained by having participants sign the eConsent via REDCap according to the established eConsent SOP and will be enrolled in the study.

Describe the circumstances under which consent will be obtained, where the process will take place and any waiting period between informing the prospective participant and obtaining consent.

All subjects will be consented by Zoom. Zoom consenting will be conducted as per the IRB-approved RU electronic Consent Process Guidelines. The subject will receive the consent form in advance of a Zoom conversation in which the study will be discussed and all questions answered. The subject will return a signed consent form to the person obtaining consent, who will then sign and date the consent form, file the original, and return a copy to the subject.

Describe the experience of the investigators designated for this task in the DOA in obtaining consent from participants.

The following staff, Joeva Barrow and Muying Li have demonstrated competency in consenting participants for participation in research studies and are certified. This competency is based on attending a consenting class which includes regulations, the do's and don'ts and didactic role playing. It also includes observing the consenting process as performed by an experienced consenter and then consenting a participant to participate in a research study while being observed by the experienced consenter.

How will it be determined that the participants or the participants' authorized representatives understand the information presented?

The "Teach Back" method will be used in the clinical research setting to ask research participants to repeat or "teach back" the information, concepts and directions that the staff member has attempted to convey to the participant. This method is used to assess comprehension and retention of protocol requirements, adverse event information, risks and benefits, and the participant's rights described in the Informed Consent process.

If English is not the participants' native language, how will written and/or verbal translation be provided?

For unexpected or isolated participants who are candidates for this study, but for whom English is not a primary language, a translator provided through Pacific Interpreters will be used to facilitate the explanation of the study, either in person or through Zoom consenting.

Will any participants be cognitively impaired so that they may not have the capacity to give consent?

○ Yes ◉ No

For participants where it has been determined that they lack the capacity to give consent, describe the provisions for obtaining consent from the participants' legally authorized representative.

Zoom consent process will be performed in accord with the RU SOP on Virtual Visits; a copy of the document is shared by Study Correspondence.

15.3 * **Based on the demographics, will this study's participant population require foreign language consent form?**

○ Yes ◉ No

15.4 * **This study's consent procedure will require the following waivers: (See Help for additional information.)**

○ Waiver of one or more elements of informed consent, 45 CFR 46.116(f)
○ Waiver of documentation of informed consent, 45 CFR 46.117(c)
◉ No waiver is requested

15.5 Will you obtain a Certificate of Confidentiality (CoC) for this study?

○ Yes ◉ No

15.6 * **Does this study include video/audio recording, photography or other electronic recording of human participants?**

○ Yes ◉ No

16.0 Recruitment and Advertising

For assistance consult CRSO to create a robust Recruitment Plan see Help.

16.1 * **What is the plan for recruitment?**

What is the plan for recruitment?

Overview: The CRROSS seeks to prescreen up to 200 healthy volunteers between the ages of 18-35 to achieve the overall goal of 120 evaluable participants.

Feasibility and Assessment:

Incentives:1) Altruism; 2) Interest in study topic 3) Compensation

Challenges: 1) Overall impact of the Covid-19 pandemic may dissuade individuals from voluntarily participating in research studies; 2) Long study visits, 3) Age eligibility of 18-35 is somewhat narrow for Type-2 diabetics and obesity 4) Compensation is modest and may need to be increased to provide greater incentive to participate.

Issues relevant to rapid accrual:

Positive: 1) Existing cohort of healthy volunteers in the repository; 2)With the exception of members of the PI's laboratory, RU employees and students are allowed to participate in the study

Negative: 1) High no-show turnout for healthy participant studies 2) Study involves visit lasting up to almost 7 hours; 3) Participants must undergo12 hour fasts and refrain from caffeine prior to the two study visits, 4) Multiple blood draws during main study visit over the course of almost 7 hours, 5)

Anticipated discomfort from the various study procedures, including prolonged cold exposure, optional punch biopsies and consuming liquid nutrition in place of solid foods during main study visit.

Projected Time to Accrual Completion (PTAC):
The research team plans to screen 2 participants 3 days per week (M-W)

Factors Affecting Predicted Time to Accrual Completion	Weeks
Volunteers will be prescreened and referred for remote consenting in advance of study visits. This should reduce no-shows and increase screen/enrollment ratio.	-----
The research team plans to screen 2 consented participants x 3 days per week to start, which translates to enrolling up to 6 participants per week (120÷6 = 20).However, given the high likelihood of screen outs due to eligibility criteria, an additional 20 weeks has been added to the predicted time frame(20+20 = 40).	40
Anticipatedstartup,add1 2weeks;ifassaynotready,addestimatedtimetoreadiness	2
Addanyvacationtimewhenscreen/visitcapacitywillbereduced	---
RecruitmentistooccurduringAugust?add2weeksduetohistoricalslowing	2
RecruitmenttooccuracrossDec Januarytimeframe;add2weeksforunitclosure	2
Knownanticipatedmaternityleave,otherLOAofkeystaff–addest.weekslostcapacity	--
StafforKSPchanges–addonboardingtime-	--
Stafftravelformajorconferences–addweekslostcapacity	--
Institutionalinterruptions(graduation,symposiumdays,etc.)addteamestimate	--
Projected Time to Accrual Completion (PTAC)	46

Recruitment Implementation:
Advertising- CRROSS will advertise on RU Classifieds, Craigslist, and ResearchMatch. Volunteers will also be drawn from the Clinical Conductor Repository.

Centralized Call Management – CRROSS will work with the research team to develop a protocol-specific pre-screening script based on IRB approved protocol eligibility criteria to prescreen volunteers who call 1800RUCARES. Potentially eligible candidates will be scheduled for the study team for further screening. CRROSS staff will also call volunteers based on Repository queries described above. Research teams are responsible to provide timely updates on pre/screening outcomes by updating volunteers' Study Status in Cerner. The Recruitment team uses screening outcomes to review progress and strategy to keep enrollment on target.

Please describe how the Recruitment Plan addresses recruitment of the volunteers consistent with the demographics of the condition under study: (referenceCensus,Maps,CDCdata)

People of all races and genders between the ages of 18-35 will be eligible to pre-screen for the study, exceptfor RU employees and students in the Principal Investigator's laboratory. RU employees and students who are not affiliated with the PI's laboratory may participate in the study if they meet eligibility requirements.

We will also be using flyers distributed around RU and surrounding areas.

16.2 *From the date of final IRB approval, how long will it take to complete enrollment of the study?

- ○ 6 Months
- ○ 12 Months
- ○ 18 Months
- ◉ 24 Months
- ○ More than 2 years (specify in years)

16.3 This Study

- ◉ Involves an intervention or comparison and a defined enrollment target
- ○ Is a natural history study with expected annual enrollment over many years
- ○ Is an exploratory mechanistic study
- ○ Other

16.4 This Study will enroll:

- ○ Healthy volunteers

○ Individuals affected with a specific disease/disorder
◉ Both

16.5 * **Do you plan on using the Research Participant Repository (RKO-0648) ?**

◉ Yes ○ No

16.6 * **Are you screening or recruiting from or through a record review of an existing patient database of a healthcare provider?**

○ Yes ◉ No

16.7 * **Please describe how the Recruitment Plan addresses recruitment of the volunteers consistent with the demographics of the condition under study:**

Through our plan to advertise locally and query the volunteer repository, we anticipate being able to enroll 120 healthy participants representative of a range of races, ethnicities and genders.

16.8 * **Do you plan to advertise directly to potential volunteers? (As opposed to relying on practitioner referrals or flyers to practitioners)**

◉ Yes ○ No

16.9 * **Do you plan to use the free, web-based volunteer registry, ResearchMatch.org, as a recruitment tool?**

◉ Yes ○ No

17.0 Research Participant Repository (RKO-0648)

17.1 This protocol, will be linked with the Research Volunteer Screening/Recruitment Data Repository run by the Recruitment staff and the Clinical Research Support Office (protocol RKO-0648-1008). In order to participate in the generation of the Repository the PI will enter into a Collector/Collaborator agreement regarding the Repository. The role of Collector/Collaborator is to contribute to the Repository the name, contact and demographic information, recruitment referral information, and screening outcome information, as well as appropriate protocol specific screening information, of volunteers who are screened by telephone or in person for entry into the protocol regardless of the screening outcome. In addition to screening volunteers for the PI's current study, verbal consent will be obtained from the volunteers regarding their willingness to be contacted in the future about possible additional research studies. This permission may be obtained by the Recruitment office staff through the central Call Center. If the PI receives calls directly from participants for initial prescreening, then the PI is responsible for collecting the required information and conveying it to the Recruitment staff for data entry. The consent or withholding of permission will be recorded in the Repository as will the name of the person who obtained the permission. A volunteer's permission or declination will not affect their eligibility for my current protocol, or future protocols. The Recruitment staff of the Clinical Research Support Office may gather the Repository information and request the verbal consent of the volunteer for re-contacting on my behalf as part of our recruitment plan. In order to benefit from the Repository, the PI will enter into a Recipient/Collaborator agreement with the Repository. The Recipient/Collaborator may receive from the Repository pre-screened lists of potentially eligible participants for his/her study as a means to facilitate recruitment. The Recruitment staff will prepare the Repository queries according to the protocol eligibility requirements and available Repository information, and may re-affirm permission to re-contact volunteers as necessary. The PI may use the information and names in the list from the Repository only for the current study and may not save the list to use for a future study of his/her own, nor may he/she share the list with colleagues for other studies."

18.0 Utilization of ResearchMatch.org

18.1 Utilization of ResearchMatch.org for Recruitment

Basic information regarding this tool:

- **ResearchMatch.org is a national electronic, web-based recruitment tool that was created through the Clinical & Translational Science Awards Consortium in 2009 and is maintained at Vanderbilt University. There is no cost for researchers at participating institutions in the ResearchMatch.org Network to use ResearchMatch.org. The Vanderbilt IRB provides oversight for ResearchMatch.org as a recruitment tool and this has been documented within the ResearchMatch.org IRB Letter of Understanding which was executed by Dr. Gotschlich in October, 2009. However, individual requests to use ResearchMatch.org as a recruitment tool must be submitted to this institutions' IRB.**

Registration:

- **This recruitment tool may be utilized once the PI or research staff registers for recruitment access through ResearchMatch.org and the Institutional Liaison provides approval.**
- **The ResearchMatch.org Institutional Liaison will review the study information and evidence of IRB approval. He/she will set the researcher's expiration date to mirror that of the study's IRB approval.**

Search Capability:

- **After being granted recruitment access, the researcher can search for appropriate matches amongst the non-identifiable ResearchMatch.org Volunteer profiles in the system. He/she can enter study inclusion/exclusion criteria in the ResearchMatch.org Search Builder which will yield a list of potential matches to the study's criteria.**

Contacting ResearchMatch.org Volunteers:

- **Once yielding a list of potential matches (ResearchMatch.org Volunteers), the researcher will send out IRB-approved content that will be the initial recruitment message that these volunteers receive about the study through ResearchMatch.org. The study's recruitment message will be inserted into the standard ResearchMatch.org electronic notification that informs possible matched Volunteers that he/she has been identified as a potential match for the study. The secure ResearchMatch.org clearinghouse will route this standard ResearchMatch.org email notification. These potential matching volunteers will have the option of replying yes, no, or not respond through a set of quick links available in this notification to the study announcement. THE CONTACT MESSAGE WILL NOT INCLUDE THE STUDY'S DIRECT CONTACT INFORMATION (e.g. EMAIL, PHONE). By responding yes, the Volunteer has authorized ResearchMatch.org to release his/her contact information to the researcher. The researcher will be responsible for managing this contact information as called for by this IRB-approved study protocol.**

Study Management in ResearchMatch.org:

- **Researchers (and the Liaison) can view information regarding his/her study's status in ResearchMatch.org (e.g. number of volunteers contacted for the study via ResearchMatch.org to date, response rate of volunteers, etc.). ResearchMatch.org will also be collecting aggregate data regarding the status of ResearchMatch.org volunteers within the study. Volunteers consent to this within the ResearchMatch.org Volunteer Agreement. This information will allow the researcher to indicate where the Volunteer currently stands within the recruitment process and thus will help the researcher monitor the utility and effectiveness of using this resource (e.g. Did not contact, Not eligible, Enrolled, Completed, etc.).**

19.0 Potential Benefits to Participants

19.1 * **Will participation in this study provide direct benefits to the participant?**

○ Yes ◉ No

20.0 Potential Risks to Participants

20.1 * **Describe any potential risks: physical, psychological, social, legal or other and assess their likelihood and seriousness. Indicate risks both to the participants and to the embryo or fetus if the participant is or may become pregnant. Please provide the potential risks below:**

Potential risks associated with venipuncture include discomfort or pain, ecchymosis, bleeding, phlebitis and infection at the needle insertion site. Additional risks include lightheadedness and a vasovagal response.

Potential risks associated with wearing a cooling jacket for 3 hours is feeling uncomfortable due to the coolness. There is a rare risk of hypothermia while wearing the cooling jacket.

Potential risks associated with an overnight fast and fasting throughout the procedure are feeling hypoglycemic and hungry.

The potential risk associated with the BodPod is feeling claustrophobic.

Potential risks of biopsy: A punch biopsy produces a small scar. Other potential side effects include pain, bleeding, or bruising at the site. Rarely a patient may develop a superficial skin infection. In people prone to keloid formation, a biopsy may heal with a keloid. Occasionally people may faint or become lightheaded during the procedure.

21.0 Procedures to Minimize Risks

21.1 * **Describe the procedures for protecting against or minimizing any potential risks, and include an assessment of their likely effectiveness. Include a discussion of confidentiality safeguards, where relevant, and arrangements for providing medical treatment, if needed.**

Venipuncture will be conducted by trained staff.

To assess for evidence of hypothermia, tympanic temperature will be monitored every 15 minutes (+/- 5 minutes) Participants will also complete a questionnaire on an iPad every 15 minutes (+/- 5 minutes) to assess their level of comfort.

The cooling vest will be worn over a hospital gown to prevent skin contact or damage. The cooling jackets used for this study have been used multiple times and have been shown to be safe. We will employ the established adaptive cooling method where the cooling temperature is set to 2^{o}C above an individual's shivering threshold.

How to minimize risk for punch biopsy: Skin/fat punch biopsy will be performed by an experienced clinician approved by the Medical Staff credentialing committee after completion of training per the RUH standard operating procedure. The procedure will be performed using sterile technique. The participant will be instructed verbally and in writing on wound care, signs and symptoms of infection, expected healing schedule, and on-call contact phone numbers. He/she will be provided wound care supplies. The participant will be contacted by the study team within 2-3 days post biopsy to monitor healing and address any concerns. Absorbable sutures rwill be used so patients will not need to return for suture removal.

A warm drink and snack will be offered after the cooling period is complete to aid with rewarming and feeling hungry.

For data protection, only coded samples and data are shared between the lab and the collaborator.

22.0 Alternative Methods or Treatments

22.1 * **Describe alternative methods or treatments for the disease(s) under study, if any, that were considered and why they will not be used:**

The study does not involve any treatments. The alternative to participation is not to participate.

23.0 Data and Safety Monitoring

This section describes the Data and Safety Monitoring Plan (DSMP) required of each protocol undertaken at the CCTS according to HRPP and NIH policies Notice 98 -084 and Notice 00-038, as cited in Help Sections below. Depending on the level or risk and trial phase, some protocols will need Data and Safety Monitoring Boards.

23.1 * Overall Risk Classification

An estimate of risk is necessary to evaluate the adequacy of the planned monitoring. The HELP section provides guidance in making the risk assessment.

Read the risk definitions and examples of risk in the HELP section and select the risk category that best describes the current study.

If your assessment differs from the definitions the HELP section, describe any factors that modify your judgment of the overall risk in the text box after the risk designation.

- ○ MINIMAL RISK
- ○ LOW RISK
- ◉ MODERATE RISK
- ○ SIGNIFICANT RISK

Please provide any optional description(s):

23.2 Protocols Involving Minors

The chance of direct benefit to the child, or to understanding a disorder not otherwise understood, may be major factors in justifying more than minimal risk in research involving children.

Based on the above definitions, please specify your study's risk classification below:

- ○ NOT GREATER THAN MINIMAL RISK (the risk of daily life to a healthy child living in a safe environment) 45 CFR 46.404
- ○ GREATER THAN MINIMAL RISK WITH DIRECT BENEFIT TO PARTICIPANT; 45 CFR 46.405
- ○ GREATER THAN MINIMAL RISK, NO DIRECT BENEFIT, BUT BENEFIT TO UNDERSTANDING OF PARTICPANT'S DISORDER; 45 CFR 46.406
- ○ RESEARCH NOT OTHERWISE APPROVED PRESENTING OPPORTUNITY TO UNDERSTAND, PREVENT OR ALLEVIATE SERIOUS PROBLEM AFFECTING CHILDREN 45 CFR 46.407 (cannot be approved by IRB; requires public comment)

23.3 DSMB

1. The NIH requires that all SIGNIFICANT RISK protocols have a **Data and Safety Monitoring Board** and provide information about the expertise and independence of that Board
2. Phase III trials require a Data and Safety Monitoring Board,
3. A DSMB may be appropriate for some Phase I and II protocols. (See Help for examples.)
4. It is the investigator's responsibility to report to the IRB, the findings and recommendations of the DSMB as they become available.

Please specify:

- ○ A DSMB is required for this study
- ◉ A DSMB is not required for this study
- ○ Unsure

If a DSMB is not required, but is being constituted for other reasons, please explain:

23.4 * Safety Review

Select one:

- ◉ Safety Review is conducted as follows: Laboratory results for research volunteers will be reviewed in a timely manner, usually within 24 hours of receipt by a licensed practitioner. The potential clinical significance of any abnormal finding will be documented in the medical and research record(s), and an appropriate plan or referral developed. The PI's review of safety issues at research team rounds will be documented in the meeting minutes.
- ○ Protocol Specific

23.5 Monitoring

Monitoring Personnel: See Help Bubble to the right.

Internal Monitoring

The PI or his/her designee shall conduct internal monitoring to assure the safe and proper conduct of the protocol and all the elements list above in monitoring, following the general principles of quality management. The intensity and frequency of internal monitoring will depend on the protocol risk to participants, the experience of the PI and research team, rate of enrollment, and specific details of the protocol.

Internal monitoring of informed consent and eligibility documentation will be conducted by the research team shortly after enrollment begins. Internal monitoring activities will be documented by logs, meeting minutes or other systematic means.

Specify the research team members who will conduct the internal monitoring of the study (see Help for who may monitor):

The PI or their designee shall conduct internal monitoring to assure the safe and proper conduct of the protocol and all the elements list above in monitoring, following the general principles of quality management. The intensity and frequency of internal monitoring will depend on the protocol risk to participants, the experience of the PI and research team, rate of enrollment, and specific details of the protocol.

Internal monitoring of informed consent and eligibility documentation will be conducted by the research team shortly after enrollment begins. Internal monitoring activities will be documented by logs, meeting minutes or other systematic means.

Specify the research team members who will conduct the internal monitoring of the study (see Help for who may monitor):
The PI will be taught how to conduct internal monitoring of her study.
For new investigators: Internal monitoring should be conducted at least monthly by new investigators until there are essentially no findings to correct at each review.

For new investigators: Internal monitoring should be conducted at least monthly by new investigators until there are essentially no findings to correct at each review.

External Monitoring

* Is external monitoring planned for this protocol?

- ○ Yes
- ◉ No
- ○ Unsure

If external monitoring is planned, please specify (see Help for who may monitor):

- ○ (Significant Risk) External monitoring will occur at least every six weeks unless there is no enrollment
- ○ (Moderate Risk) External monitoring will occur at least quarterly
- ○ (Low or Minimal Risk) External monitoring will occur at least annually

If external monitoring is planned, please specify the name of the monitor:

- ☑ Note that copies of external monitoring reports must be supplied to the IRB and the CRSO as soon as they are made available

Additionally, audits of the research records of minimal, moderate or significant-risk protocols may be performed by the CRSO staff on a random basis or as part of a prospectively identified auditing plan.

23.6 Adverse Event Classification

Adverse events are classified by definition, severity, and association with the investigational trial.

Definition of an Adverse Event
Any unfavorable or unintended sign (including abnormal lab findings), symptom or disease temporally associated with the use of a medical treatment or procedure, or protocol, regardless of whether it is considered related to the medical treatment or procedure or protocol.

Definition of a Serious Adverse Event
Any unanticipated event that involves the following:
- o results in death
- o is life-threatening
- o requires hospitalization or prolongs existing hospitalization
- o results in persistent or significant disability/incapacity
- o is any medical event which requires treatment to prevent one of the outcomes listed above

Other events can be classified as "serious adverse events" at the discretion of the PI.

Definition of Anticipated/Expected Adverse Event

Any adverse event, which has been reported in the Investigator's Brochure, package insert, safety reports, clinical protocol, consent form or listed in the NCI agent-specific Expected Adverse Event List[3], is classified as an expected adverse event. The investigator must provide the available data of known adverse events and toxicities that have been associated with the study drug, device, intervention, or procedures. This information helps to define the level of risk of the trial and enables safety monitoring. A minimal risk trial may not have any defined risks and a statement to that effect is sufficient to meet the DSMP requirements.

Definition of an Unanticipated/Unexpected Adverse Event
Any adverse event that is not consistent with the known, predicted possible effects of the research protocol. An unexpected adverse event varies in nature, intensity or frequency from information on the investigational product provided in the Investigator's Brochure, package insert, safety reports, clinical protocol, or listed in the consent form.

Definition of an Unanticipated Problem (UaP)
A UaP is an event or circumstance that meets all the following three criteria: [1] the nature, severity, frequency of the event(s) or information was not expected in the descriptions in the study documents or the characteristics of the participant population being studied; [2] there is a reasonable possibility that the procedures involved in the research caused or are linked in a significant way to the problem; [3]the event or information suggests that the research places particpants or others at a greater risk of harm than was previously known or recognized (including physical, psychological, economic, or social harm.

Grade and Relatedness of Adverse Events:

Adverse Events are graded for severity and scored for relatedness to the protocol, according to a published scale. Several standardized AE Reporting scales are available. (See Help for links to these scales.)

* Please indicate the scale you intend to use:

- ○ CTC v2.0 (http://ctep.info.nih.gov/reporting/ctc.html)
- ○ CTCAE v3.0 (http://ctep.info.nih.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf)
- ○ CTCAE v4.0 (http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf)
- ◉ CTCAE v5.0 (https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf)
- ○ AIDS Clinical Trials Group (http://aactg.s-3.com/)
- ○ Other

23.7 Reporting Adverse Events

All AEs will be reported to the IRB at least annually.

Reporting Serious AEs

☑ Serious Adverse Events, (SAEs) will be reported to the IRB according to policy, within two working days of identification of the SAE.

Select all that apply:

☐ SAEs will be reported to the Sponsor and or ESCROW

SAEs will be reported to the sponsor within how many days of the event?

☐ SAEs will be reported directly to the FDA, per 21 CFR 312

SAEs must be reported directly to the FDA within 7 days of the event by the investigator/sponsor.

☐ SAEs will be reported to another entity

Describe:

Reporting Unanticipated AEs:

Select all that apply:

☑ UAEs will be reported to the IRB

UAEs that are related and greater than moderate severity must be reported to the IRB according to policy, within two working days of identification of the UAE.

☐ UAEs will be reported to the Sponsor

UAE will be reported to the sponsor within how many days of the event?

☐ UAEs will be reported to the FDA, per 21 CRF 312

UAEs will be reported to the FDA, per 21 CRF 312, within 15 days.

☐ UAEs will be reported to another entity

Describe:

23.8 Reporting Unanticipated Problems

☑ Unanticipated problems involving risks to participants or others will be reported to the IRB and the CRSO within five working days.

23.9 CLIA/CLEP

Only laboratory and research tests that are CLIA/CLEP certified or waived may be used to determine eligibility, shared with research volunteers, and used in clinical decision making.

Select if applicable:

☑ This study includes tests that are not CLIA/CLEP certified; the results of such tests will not be used in clinical decision making, or to determine eligibility, or shared with participants or their health care providers.

23.10 Tissue Repository

Human Tissue and Data Repositories collect, store, and distribute human tissue materials and or data for research purposes. Repository activities involve three components: (i) the collectors of tissue samples\data; (ii) the repository storage and data management center; and (iii) the recipient investigators.

* Select one:

◉ I DO NOT intend to collect, store, and distribute human tissue materials for research purposes

○ I DO intend to collect, store, and distribute human tissue materials for research purposes, therefore this protocol entails the Operation of a Tissue Repository. The IRB requires that the protocol specify the conditions under which data and specimens may be accepted and shared, and ensuring adequate provisions to protect the privacy of participants and maintain the confidentiality of data.

If you do intend to collect, store, and distribute human tissue materials, you will be asked to upload the following documents later on in the submission:

- A Sample collection protocol (for tissue collector collaborators to follow) and informed consent document for distribution to tissue collectors and their local IRBs.
- A Certificate of Confidentiality (to protect confidentiality of repository specimens and data).
- A Recipients Agreement describing the commitment of the recipient to preserve the anonymity of the samples shared.

24.0 Toxicity Management and Stopping Rules

24.1 * Describe any drug toxicity or other conditions under which the participation of a participant or the conduct of the study would be stopped in order to maximize safety (e.g., toxicity management and stopping rules):

The study will be stopped for safety reasons related to symptomatic hypothermia (e.g., shivering, slurred speech or mumbling, shallow breathing, weak pulse, clumsiness, or loss of coordination, drowsiness, or confusion.

*** Indicate withdrawal criteria and procedures below:**

If the participant exhibits any major discomfort or hypothermia, the experiment will be stopped, the cooling jacket removed, and the participant will be warmed with blankets.

The participant will be withdrawn from the study if the participant's temperature reaches 35.5 degrees Celsius.

25.0 Compensation/Costs

25.1 *Will any compensation be offered to participants in return for their participation, e.g., direct payment, medical care, tests, etc.?

○ No

◉ Yes (Please describe)

Please Describe

Participants will be compensated up to $300 upon completion of the study, participants who complete both biopsies will receive an additional $100 in cash.

25.2 * Will there be any costs to participants associated with their participation in research?

○ Yes ◉ No

26.0 Bibliography

26.1 Enter your bibliography below:

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27.0 Appendices

27.1 Enter your appendices below:

28.0 Funding

28.1 * Do you have sufficient financial resources to support your study?

(•) Yes ( ) No

28.2 If this study is/was pilot funded, please specify dates of funding:

From date:

To date:

28.3 Source of investigational agents:

(•) N/A (no investigational agents)

- ○ Provided by a pharmaceutical sponsor/partner with funding as described below
- ○ Provided by a pharmaceutical sponsor/partner without additional funding
- ○ Provided by investigator, participants, or other

28.4 Specify funding by Rockefeller University, industry sponsor and/or grant:

Search for a sponsor

	Sponsor	Funding
Rockefeller University	Paul Cohen Laboratory.	☑
Industry		
Grant		
Pilot Award		

28.5 List grants in which this study is named:

	PHS or Non-PHS	Program	Grant Number	Grant Name	From Date	To Date
No results found						

29.0 Clinical Services

29.1 *What is the general health status of your study group(s)?

- ☑ Well/Minimally Ill
- ☐ Moderately Ill
- ☐ Severely Ill
- ☐ Other
- ☐ Not Applicable

If other than Well/Minimally Ill, please describe:

29.2 * Does your study group have special care needs?

○ Yes ◉ No

29.3 * Does your study have special equipment needs?

◉ Yes ○ No

If Yes, please describe:

Polar Cooling jacket; provided by the research team.

29.4 * Will you require storage space on the clinical units for supplies to conduct this study?

◉ Yes ○ No

If Yes, please describe:

Cooling jacket stored in locked closet on the RUH unit.

29.5 * Is special training of hospital staff required?

○ Yes ◉ No

30.0 Pharmacy Services

30.1 * Does the study require Pharmacy Services?

○ Yes ◉ No

31.0 Bionutrition

31.1 * Will study require patient meals?

◉ Yes ○ No

If Yes, please specify:

Type of Diet	In/Outpatient	Pack Meal
Standard	☐ Inpatient ☑ Outpatient	○ Pack Meal
Therapeutic	☐ Inpatient ☐ Outpatient	○ Pack Meal
Research Diet	☐ Inpatient ☐ Outpatient	○ Pack Meal
Formula Diet	☐ Inpatient ☑ Outpatient	○ Pack Meal

Nutrient(s) to be controlled (specify):

Visit #1: The BodPod will be ordered for the participant on visit 1. The BodPod will be the first scheduled procedure on visit 1. It will be conducted first thing in the morning, about 9 am.
The participant will have an in.pt. hot breakfast and hot lunch ordered. Bionutrition will administer either meal, as requested.

Visit #2. The Barrow research team will then formulate an individualized tailored nutrition beverage that will meet 33% of each participants' daily EER. This nutrition beverage (Katefarm Nutrition Shake which is USDA Organic, Non-GMO, plant-based, vegan, and does not contain milk, eggs, fish, shellfish, tree nuts, peanuts, wheat, or soybeans https://vpn.rhttps://shop.katefarms.com/products/nutrition-shake) will be provided to participants on Visit #2 to ensure that study participants are maintained at nutrient baseline and maintained in a fed state throughout the study. The formula will be provided to Rockefeller Bionutrition department, by the Barrow research team, for storage, preparation and administration.

31.2 Will meal times be altered?

◉ Yes ○ No

If Yes, please explain:

Meals will be offered whenever the participant is ready for them.

31.3 Does the protocol require any of the following activities?

☐ Food Frequency Questionnaire
☑ Bod Pod/ Anthropometric Measurements
☑ Diet History/ Food Records
☐ Diet/ Nutrition Education

31.4 Will food be provided to caregiver, parent or significant other?

○ Yes ◉ No

31.5 For metabolic diets, is diet homogenization required for nutrient analysis by independent lab?

○ Yes
○ No
◉ N/A

32.0 Clinical and Translational Research Facilitation Office

32.1 Indicate navigation assistance requested and/or received in the development of the study:

	Requested	Received
Protocol Development	☑	☑

Protocol Implementation	☑	☑
Protocol Conduct	☑	☐
ACCTS/IRB Submission	☑	☑

32.2 Indicate additional education assistance requested and/or received in the development of the study:

	Requested	Received
IND	☐	☐
IDE	☐	☐
Team Science Education	☑	☑
Study Progress Meeting	☐	☐
Investigator Responsibilities	☑	☐
Regulatory Binder/Folder	☑	☑
Source Documentation	☑	☐
Participant Involvement in Research	☐	☐

33.0 Clinical Research Support Office Resources (CRSO)

33.1 Indicate regulatory input assistance requested and/or received in the development of the study:

Regulatory Support/Design	Requested	Received
General, Vulnerable Populations, Minors, Group Harms	☐	☐
IND/IDE advice, assistance, and referral	☐	☐
Informed Consent/Assent	☐	☐
Data Safety Monitoring Plan	☐	☐
Clinical Trial Registration	☐	☐
Plan For Return of Research Results	☐	☐
Audit/Monitoring Service, Referrals, SOPs	☐	☐

33.2 Indicate recruitment assistance requested and/or received in the development of the study:

Recruitment of Participants	Requested	Received

Recruitment Planning and/or written Plan	☑	☑
Advertising Strategy, Content, Placement	☐	☐
Repository/Research Match Queries	☐	☐
Call Center/Prescreening/Scheduling	☐	☐
Cost Sharing for Advertising	☐	☐

33.3 Indicate community engaging assistance requested and/or received in the development of the study:

Community Engagement	Requested	Received
PHI Statement/Engaging Stakeholders Section	☐	☐
CEnR Navigation – fostering pt/community partnership	☐	☐
Outreach to community/partner/advocacy group/CE Studio	☐	☐

33.4 Indicate other assistance requested and/or received in the development of the study:

Other	Requested	Received
Survey design, fielding, validation	☐	☐
Data transfer and security planning	☐	☐

34.0

BERD: Biostatistics, Epidemiology and Research Design Resource

34.1 Indicate the Biostatistical assistance requested and/or received in the development of this study:

	Requested	Received
Development of experimental design	☐	☐
Power analysis/Sample size determination (# of subjects)	☐	☐
Navigation (Did Statistician participate in a navigation meeting)	☑	☑
Randomization schedule	☐	☐

Data analysis	☐	☐
Development of new statistical techniques for data analysis (Statistical research)	☐	☐
Protocol implementation	☐	☐
Other	☐	☐

34.2 If you are/will be using data analysis specify:

- ☐ Exploratory
- ☐ Descriptive
- ☐ Hypothesis testing
- ☐ Statistical modeling
- ☐ Other

34.3 If you are/will be assisted with protocol implementation, specify:

- ☐ Publication
- ☐ Conference
- ☐ Other (type of dissemination)
- ☐ Grant(s)

34.4 Please select the Biostatistician on this Protocol:

- ☑ Roger Vaughan, DrPH
- ☐ Caroline Jiang, MS
- ☐ Sandra Garcet, PhD
- ☐ Adam Qureshi, MA
- ☐ Other

35.0 Biomedical Informatics Resources

35.1 Indicate Bioinformatics assistance requested and/or received in the development of this study:

	Requested	Received
Microarray analysis	☐	☐
Pathway analysis	☐	☐
RNA-seq analysis	☐	☐
Bioinformatics training and consultation	☐	☐
Bioinformatics experimental design	☐	☐
HPC computing	☐	☐
Other	☐	☐

35.2 If you are/will be using pathway analysis software, specify:

- [ ] Ingenuity IPA
- [ ] David
- [ ] GSEA
- [ ] Other

35.3 If you are/will be using RNAseq analysis software, specify:

- [ ] Tophat
- [ ] Cufflinks
- [ ] Cuffdiff
- [ ] CummRbund
- [ ] STAR
- [ ] featureCounts
- [ ] DESeq2
- [ ] VOOM
- [ ] RNA-SeQC

If other, specify:

35.4 Indicate Medical Informatics assistance requested and/or received in the development of this study:

	Requested	Received
Data storage inside of iRIS	☐	☐
Redcap Database	☐	☐
Custom or Ad Hoc reports	☐	☐
Study plan creation	☐	☐
Specialize database or custom software	☐	☐
Other	☐	☐

36.0 HIPAA Form

36.1 A study's specific HIPAA form signed by the volunteer is required for institutions that are HIPAA covered entities so that they may communicate Private Health Information (PHI) to the Investigator.

Below, Memorial Sloan Kettering Cancer Center, New York-Presbyterian Hospital and Weill Medical College of Cornell University are listed so that that they may report laboratory results and X-ray readings respectively. If you foresee that any other entity may need to provide PHI then add them to the field highlighted in green.

36.2 Name of Study:

Identification of thermogenic silencing regulatory factors as biomarkers of metabolic health in humans

36.3 Principal Investigator:

Paul Cohen, MD, PhD

36.4 Industry Sponsor:

If the funding source is industry please type in the sponsor here

Who may obtain, use, and/or disclose your health information?

The following persons and organizations may obtain, use, or disclose health information about you.

- The Principal Investigator(s) listed at the top of this form, and persons who assist the Investigator(s) in carrying out the research
- Each research site for this study, including The Rockefeller University, and the research management and support staff and the medical staff at each site
- Health care providers who have provided in the past, or currently provide, health care services to you
- Laboratories and other persons and organizations that will analyze your health information and/or biological samples as part of this study, including Memorial Sloan Kettering Cancer Center, New York-Presbyterian Hospital and Weill Medical College of Cornell University

Other entities that may need to provide PHI:

Cornell University- Ithaca, NY

- Members and staff of the Institutional Review Board and other boards and committees that watch over research at The Rockefeller University
- Members and staff of The Rockefeller University's Office of Sponsored Research
- The sponsor(s) of the research, named above, and persons who watch over the research for the sponsor(s)
- The United States Food and Drug Administration, other government agencies, regulatory entities and Rockefeller University consultants that watch over the safety, effectiveness, and quality of research and/or fund The Rockefeller University Hospital
- Others (as described here):

What information will be obtained, used, or disclosed?

The persons and organizations listed above may obtain, use, and disclose:

- Information about you that is created or collected during the research study (but not including any HIV-related information)
- Health information in your medical records that is relevant to the research study (but not including any HIV-related information)
- **And**, if checked below:

___ HIV-related information (this includes any information indicating that you have had an HIV-related test or have HIV infection, HIV-related illness, or AIDS, as well as information that could indicate you may have been exposed to HIV)
___ Other information (as described here):
_____
_____
_____
_____

- Other information (as described here):

By signing this form, you give permission to the persons and organizations listed above to obtain, use and disclose your health information noted above.

How will your health information be used?

The health information noted above, as well as information shown by the boxes checked above (if any), may be obtained, used, and disclosed:

- to conduct the research study explained to you during the informed consent process; and
- to assure the quality, safety, and effectiveness of the research study

Please note that the persons and organizations listed above may re-use or further disclose your information if they are permitted by law to do so.

What are your rights?

It is your right to refuse to sign this authorization form. If you do not sign this form, you will not be able to participate in the research study. Your health care outside the study will not be affected. The payment for your health care and your health care benefits will not be affected.
If you sign this authorization form, you will have the right to withdraw it at any time except to the extent that the persons and organizations listed above:

- have already taken action based upon your authorization;
- need the previously collected information to complete analysis and reports of data for this research; or
- will continue to use and disclose previously collected information as permitted by the informed consent form signed by you (except as to HIV-related information, for which disclosure to new persons or organizations will not occur unless permitted by federal or state law).

If you withdraw the authorization, you will not be permitted to continue taking part in the research study. This authorization form will not expire unless you withdraw it. If you want to withdraw this authorization, please write to the above named investigators.
You have a right to see and copy your health information described in this authorization form in accordance with The Rockefeller University's policies; in certain circumstances where the integrity of the study will be affected, you will not be able to obtain your health records in this study until the study has been completed.
You will receive a copy of this form after you have signed it.

Notice Concerning HIV-Related Information

If you are authorizing the release of HIV-related information, you should be aware that such information may not be shared without your approval unless permitted by federal or state law. You also have a right to request a list of people who may receive or use your HIV-related information without authorization. If you experience discrimination because of the release or disclosure of HIV-related information, you may contact the New York State Division of Human Rights at (212) 480-2493 or the New York City Commission of Human Rights at (212) 306-7450. These agencies are responsible for protecting your rights.

Your signature

I have read this form, and all of my questions have been answered. By signing below, I acknowledge that I have read and accept all of the information above.

_____
Signature of participant or participant's legal representative

_____
Date

_____
Printed name of participant

_____
Printed name of legal representative (if applicable)

_____
Representative's relationship to participant

THE STUDY PARTICIPANT OR HIS OR HER PERSONAL REPRESENTATIVE MUST BE PROVIDED WITH A COPY OF THIS FORM AFTER IT HAS BEEN SIGNED.

37.0 End of Application Form

37.1 The study application form is complete.

The next step in the submission process is to gather attachments before proceeding to the submission form.

The following submission reports are generated in the Lab/Dept Reports menu, Submission Reports section:

- **Delegation of Authority** (if applicable, and if not previously generated)
- **HIPAA form** (if applicable)
- **CCTS Utilization Report** (required for all submissions)
- **Study Progress Report** (if the study has been managed in iRIS for a minimum of one year, generate the Progress Report from the report menu in iRIS. if the study has not been managed in iRIS for one year, complete the Progress Report located on the IRB website.)

All other required forms can be downloaded from the corresponding sections' help links above or from the IRB website.