September 24, 2024

Ketone Supplementation in Cystic Fibrosis

NCT 04938726

To Whom it May Concern,

Please find the Study Protocol included in this information.

Eric P. Plaisance

INTEGRATED RESEARCH ADMINISTRATION PORTAL

IRB ePortfolio

1. GENERAL QUESTIONS

Protocol Number IRB-300007323

Principal Inves. gator Name Plaisance, Eric P.

Title of proposed project:

Ketone Monoester Supplementation in Cystic Fibrosis: A Pilot and Feasibility Study

* Select the type of application you are submitting to the IRB for review. Continuing Review

NOTE: The ePortfolio should NOT be used for Continuing Reviews for protocols not INITIALLY submitted on the ePortfolio. Please see instructions for submitting the appropriate form here.

The OIRB has developed a list of . ps and best pracĀces for IRB submissions. Review the document here for assistance in developing your application.

Initial IRB Protocol Application

* **PURPOSE:** In non-technical, lay language, provide the purpose of the project. The contents of this section are copied to other areas of IRAP. As such, provide **only** the purpose of the project here.

Assess the acceptability and tolerability of an exogenous ketone monoester supplement and determine its effects on reducing markers of inflammation in the lungs and improving clinical outcomes for patients with cystic fibrosis. The exogenous ketone that will be used in this study is a commercially available nutriĀonal supplement known as KE4 from KetoneAid, Inc. Biomarkers of inflammation and nutrition will be analyzed in the blood and sputum samples.

BACKGROUND: In 2-3 paragraphs, summarize the past experimental/clinical findings leading to the design of this project. Include any past or current research that informed the study design and any previous results that are relevant to understanding the project. Lastly, list the study outcomes that will be measured to evaluate the purpose of the project . It is not necessary to include methodology in this secĀon. NOTE: Technical terms must be defined in simple language. Abbreviations must be spelled out. Provide references for any specific citations.

Our group has investigated the physiological and metabolic responses to a number of exogenous ketone supplements in both rodents and humans. Our experience and that of our colleagues lead us to the conclusion that exogenous ketone supplements provide an exciting approach to increase circulating ketone concentrations. These findings suggest that administration of exogenous ketones might hold promise in reducing inflammation in a number of chronic disease conditions that cause inflammation, including CF.

METHODS: Describe the procedures for all aspects of your protocol. Tell us what you are doing.

Participants will be recruited by the Principal Investigator or Study Coordinator from the inpatient and outpatient CF population at UAB. Following admission to UAB Hospital for a routine CF exacerbation, or within the outpatient setting, the Study Coordinator will discuss the study with participants and obtain written informed consent before initiating the study.

Patients will be randomly allocated in unbalanced numbers (2:1) (n = 15 ketone and n = 8 control) to receive a ketone monoester or an identical-tasting placebo, respectively, for 8 days during the course of hospitalization for treatment of acute pulmonary exacerbation (One, 60 mL bottle of either a ketone ester will be consumed twice daily (30 mL or 15.0 g per dose) (KE4, KetoneAid, Falls Church, VA; 15.0 g or placebo (PL, flavored to closely match taste of the ketone) will be administered following an overnight fast and again at 1500h.

Participants will be asked to drink about 1 fluid ounce of the ketone or placebo supplement twice a day (once in the morning and once mid-late a ernoon) for up to 7 days. Each day in the study, the participant will be asked to fast overnight for about 8 hours before drinking the first dose of ketone or placebo. Following administration of the first dose of either the ketone or placebo and on either day 5, 6, or 7 a small drop of blood will be obtained from their finger before (time 0 min) and 15, 30, 60, 90, and 120 min a er drinking the supplement. On days in between visit 1 and visit 2, we will check their blood sugar before drinking the supplement and 30 minutes a er they drink the supplement. We will use a commercially available ketone meter (Keto-Mojo, Napa, CA) that provides a rapid assessment of blood ketone and glucose (sugar) levels. The Keto-Mojo device requires a finger stick with a lancet, identical to those used to measure blood sugar, and uses only a small drop of blood. Patients will be educated on how to use the device and self measure ketone and blood sugar.

Blood sampling will occur from their indwelling catheter or venipuncture at day 1 and at day 5, 6, or 7 before administraĀon of the ketone or placebo. We will try to coordinate this with any blood sampling done for clinical care.

The Keto-Mojo device requires a finger stick with a lancet, identical to those used to measure blood sugar, and uses only a small drop of blood. The device provides values within about 15 seconds following sampling. An alcohol prep will be used to cleanse the surface of the skin prior to each stick and a bandage will be applied to reduce risk of infection.

Participants will remain on all CF chronic care medications and/or standard exacerbation therapy (intravenous antibiotics and increased airway clearance throughout the course of the study. The study pharmacist will provide the ketone or placebo supplements by computer-generated random assignment in blocks of three participants and will have sole access to the randomization code.

Spirometry measurements, CRP, and, history/physical exam and Sputum bacteriology will be conducted at the beginning of hospitalization as part of standard of care (these results will be pulled from the medical record for study purposes. Spirometry measurements and history/physical exams will also be performed at the end of hospitalization as part of standard of care and will be pulled from the medical record for study purposes.

For outpatient subjects, these results will be pulled from the medical record and study procedures will also be perfomred at visit 1 and visit as according to the consent

Spirometry will also be be per formed in addtion to those for standard care just before the participant drinks the ketone supplement or placebo control and one hour after on day 1 and either day 5, 6 or 7.

Additional sputum and blood will be collected at baseline before the treatment and at patient-discharge for trial-specific readouts.

The participants will also be asked to complete the CFQR questionnaire and a food diary every night. They will also be asked to complete the symptom questionnaire on hour a er receiving the morning ketone or placebo.

REQUIRED - SELECT ONE OR BOTH: Will this be a retrospective study and/or a prospective study?

☐ Yes ☑ No * Retrospective

☑ Yes ☐ No * Prospective

☑ Yes ☐ No * Will the study involve the prospective collection or analysis of data, documents, or records?

☑ Yes ☐ No * Will the study involve the prospective collecÃon or analysis of biospecimens?

What is the expected end date of the study (including data analysis)? 01-May-2023

* Provide the total number of subjects to be included at all sites, both retrospectively (including records) and prospectively. 25

* Provide the total number of subjects to be included at UAB, both retrospectively (including records) and prospectively. 25

Select the status of the Principal Investigator.

☑ Faculty/Staff

☐ Student/Trainee

☐ Yes ☑ No Are any of the investigators listed on the IRB Personnel Form students using this research for their capstone project, thesis, or dissertation?

☐ Yes ☑ No Is the project to be conducted internationally?

Procedure List

Select all study procedures and indicate whether the procedures are research only or routine.

Procedure	Select whether the procedure is research or routine.
Blood drawing	Protocol Driven
Biological sampling (other than blood)	Protocol Driven
Placebo	Protocol Driven
Randomization	Protocol Driven
Pregnancy testing	Protocol Driven
Record review (which may include PHI)	Protocol Driven
Placebo	Protocol Driven
Physical Exam	Protocol Driven
Surveys, questionnaires, or interviews (one-on-one)	Protocol Driven
Diet, exercise, or sleep modifications	Protocol Driven
Food supplements	Protocol Driven

☑ Yes ☐ No Does the protocol involve any procedures not described in the above table?

Describe the procedure(s), including whether the procedure(s) are research only or routine.

spirometry- protocol driven

Research Area

Select the type of research.

☑ Biomedical (non-oncology)

☐ Behavioral (non-oncology)

☐ Oncology

2. CONTINUING REVIEW

Project Information

Starting date of project 01-Sep-2021

Current IRB expiration date 10-Oct-2024

☐ Yes ☑ No Do any of the investigators have a financial conflict of interest management plan issued from the Conflict of Interest Review Board?

Indicate the status of your study.

☐ Not yet open

☐ Open

☐ On hold

☑ Closed to enrollment 30-Apr-2023 * Date enrollment closed

☐ On protocol procedure

☐ In long-term follow-up

☑ In data analysis only

☐ Completed

Provide the number of subjects currently active in the study (receiving study intervention, active follow-up, etc.). NOTE: Enter 0 if the study only involves secondary data analysis.

Participant Group/Sub-study/Site	Number AcĀve

Total number of acĀve participants.

Provide the number of subjects enrolled since the start of the study by participant groups, sites and/or sub-study. NOTE: Enter 0 if the study only involves secondary data analysis.

Participant Group/Sub-study/Site	Number Enrolled

Total number of parĀcipants enrolled since the start of the study 15

Provide the number of subjects enrolled since the last continuing review by participant groups and sub-study.

Participant Group/Sub-study/Site	Number Enrolled Since Last Continuing Review

Total number of participants enrolled since the last continuing review 0

☑ Yes ☐ No Are there preliminary results from the study?

Provide the preliminary results from the study.

Preliminary analysis suggests that patients tolerated the ketone ester well with no adverse effects. We also show that the ketone ester increases circulating ketone concentrations and decreased sputum and some plasma inflammatory markers. There were no significant effects on pulmonary function as measured by spirometry, but patients did report an improvement in their perception of respiratory function as determined by the CFQ-R

☐ Yes ☑ No * Has there been any new substantive literature relevant to the risks, procedures, or interventions of the study?

☐ Yes ☑ No * Since the last IRB review, has your study received an audit by an internal or external group (e.g., UAB for-cause audit or government entity)? NOTE: This does not include study team self-audit, sponsor monitor visits, or sponsor audits.

☐ Yes ☑ No Have there been any changes to the study since the last continuing review? If there has been no continuing review, have there been changes to study acĀviĀes since the iniĀal review?

Prospective

☐ Have any UAB subjects voluntarily withdrawn or been administratively withdrawn since the last IRB review?

☐ Yes ☑ No * Over the life of the protocol, have there been any Serious Adverse Events (SAEs)/unanticipated problems, and/or unanticiapted problems?

☐ Yes ☑ No * Over the life of the protocol, have there been any problems NOT meeting the UAB criteria for reportable problems but the sponsor requests IRB notification?

☐ Yes ☑ No * Have there been any protocol deviations since the last IRB approval, including both previously reported and unreported?

☐ Yes ☑ No Has there been an IND Annual Report submitted to the FDA since the last approval?

Indicate whether any of the following have occurred since the last IRB Approval.

☐ You have had one or more problems obtaining informed consent.

☐ You have received complaints about the research.

If you wish to add any information for the IRB to consider (e.g., any information the IRB has not already asked for or the research team has not already provided and the research team believes will aid the IRB in their review), provide it here.

☐ Yes ☑ No * Is this a mulĀ-site study?

Provide the number of subjects screened and enrolled at UAB since the last IRB review.

0 Total screened

0 Total enrolled

Complete the table for participants who are not of Hispanic or LaĀno ethnicity.

Racial Categories	Female	Male	Unknown/Not Reported
White	7	7	
Black or African American	1	0	

Complete the table for participants who are of Hispanic or LaĀno ethnicity.

Racial Categories	Female	Male	Unknown/Not Reported

Complete the table for participants whose ethnicity is unknown or not reported.

Racial Categories	Female	Male	Unknown/Not Reported	

5. RESEARCH DETERMINATION

Research Determination Form

☑ Yes ☐ No * Is the acĀvity a systematic investigation?

☑ Yes ☐ No * Is the acĀvity designed to develop or contribute to generalizable knowledge?

☑ Yes ☐ No * Does the project involve obtaining information about living individuals?

☑ Yes ☐ No * Does the project involve an intervention or an interaction with parĀcipants?

☐ Yes ☑ No * Does the project involve an FDA regulated test article?

☑ Yes ☐ No * Is the project defined as a clinical investigation?

Briefly describe the proposed project, including what materials are being obtained and their sources. **If you provided this information on Page 1 (General Questions), enter "See above."**

Spirometry measurements, CRP, and, history/physical exam and Sputum bacteriology will be conducted at the beginning of hospitalization as part of standard of care (these results will be pulled from the medical record for study purposes. Spirometry measurements and history/physical exams will also be performed at the end of hospitalization as part of standard of care and will be pulled from the medical record for study purposes.
AddiĀonal spirometry, queasƟonaire, sputum and blood will be collected at baseline before the treatment and at patient-discharge for trial-specific readouts for out patients medical history will also be pulled from the medical record

Risk Level - FDA Regulated

* **REQUIRED: Select whether the project involves minimal risk or greater than minimal risk to participants.**
Greater than Minimal Risk

Sources of Private Information

Indicate the information that may be obtained, accessed, used, disclosed, or shared from an individual (living or deceased). Select all that apply.

☐ An individual's genetic tests

☐ Genetic tests of family members of a particular individual (including an embryo or fetus)

☐ Genetic manifestation of a disease or disorder in family members of a particular individual

☐ Any request for, or receipt of, geneĀc services, or parĀcipaĀon in a clinical study which includes geneĀc service, by the individual or any family member of the individual

☐ Education records of an individual

☐ Alcohol or substance abuse information, including diagnosis, treatment, or referral of treatment for alcohol abuse, substance abuse, or chemical dependency

☑ Yes ☐ No Will the PI or others obtain, review, or make other use of participants' "protected health information" (i.e., information, whether oral or recorded in any form or medium that (a) is created or received by a health care provider and (b) relates to past, present, or future physical or mental health or condition of an individual; or provision of health care; or payment for provision of heath care)?

☐ Identifiable, but not private, information

☐ Other identifying information

☐ Yes ☐ No * Is the project subject to the 2023 NIH Data Management and Sharing (DMS) policy?

☐ Yes ☑ No * Will information be received from outside of UAB?

☐ Yes ☑ No * Will you share the information with an institution other than UAB?

☐ Yes ☑ No * Will you need to obtain information from a department other than your own?

Provide any additional information for the IRB to consider. Upload any relevant files in the Attachments section.

6. NON-AFFILIATED PERSONNEL

Non-UAB/CoA Personnel

☐ Yes ☑ No * Are there any NON UAB, Children's of Alabama (CoA), Lakeshore Foundation, or Birmingham Veteran's Affairs Medical Center (BVAMC) key personnel on this study? NOTE: UAB, CoA, Lakeshore Foundation, and BVAMC investigators must be listed on the IRB Personnel Form. Additionally, this page does not apply to adding sites for Single IRB or mulĀ-site research.

7. SPONSORS AND ENTITIES

Funding, University Contracts, Subcontracts, MTAs, or DUAs

☑ Yes ☐ No * Is this project funded in any way?

☑ Yes ☐ No * Is the funding internal?

☐ Yes ☑ No Does the project involve any University Contracts, MTAs, DUAs, or subcontracts/subawards? NOTE: Subawards are identified by the OSP Assigned Number with a three digit suffix (e.g., 000500000-001).

☐ Yes ☑ No Will the project receive non-monetary support (i.e., drugs, devices, services, etc.) from another enĀty?

9. PROSPECTIVE

☑ Yes ☐ No * Drugs/Dietary Supplements

☐ Yes ☑ No * Biologics

☐ Yes ☑ No * RadiopharmaceuĀcals

☑ Yes ☐ No * Medical Devices

☐ Yes ☑ No * In-vivo imaging, image guided intervenĀons (e.g., CT, PET/CT, MRI, PET/MRI, x-ray, DEXA, fluoroscopy, nuclear imaging, ultrasound) or radiation therapy

☐ Yes ☑ No Is this a mulĀ-site study?

☑ Yes ☐ No Does the study involve access, review, or disclosure of Protected Health Information (PHI) ?

☑ Yes ☐ No Does the study involve randomization?

Include the risks and benefits of randomization in the consent form.

☑ Yes ☐ No Does the study require clinical services at any of these sites?

☐ Yes ☑ No Will any of the services be billed to either parĀcpants or to the study account through the Hospital Billing Office (PFS) or the HSF Billing Office (MSO)?

☐ Yes ☑ No Will this study involve direct interaction with participants who have an infectious disease?

Target Accrual Information

35 Approximately how many subjects will need to undergo screening procedures to determine whether they qualify to be enrolled? Enter 0 if not applicable. NOTE: This number is an approximation based on previously completed projects.

25 How many subjects do you intend to enroll at UAB? Enter 0 if not applicable.

Describe how the screening and enrollment numbers above are determined (e.g., provide a power analysis, explain the pilot data, or reference prior studies.

UAB Hospital admits approximately 70 unique cases each year and has a outpatient population of around 250 patients, so we anticipate, over the 2-years of funding, we will have the appropriate number of patients available to address our questions.

What are the target age range(s) of the potential subjects with which you will interact?

1. <18 ☐
2. 18-89 ☑
3. >=90 ☐

Indicate which of the following populations you will be **targeting** (enrolling, interacting, or intervening with) for your study. Select all that apply.

☐ CogniĀvely impaired adults

☐ Economically or educationally disadvantaged

☐ UAB employees

☐ Fellows

☐ Individuals with Limited English Proficiency (LEP) or non-English speakers. Recruitment of study with LEP or non-English speakers is generally required, if the study holds the prospect of a direct therapeutic benefit to the participant.

☐ Individuals of specific racial, religious, or ethnic groups

☐ Individuals living outside the 50 US states

☐ Pediatric and neonates

☑ Patients (This includes existing patients)

☐ Persons who are institutionalized

☐ Pregnant women or fetuses

☐ Prisoners

☐ Medical Residents

☐ Study Staff or investigators named on this application

☐ Students

☐ Others

☐ None of the above, not targeting specific populations

How will the study team identify potenĀal subjects? Select all that apply.

☐ Non-UAB physicians ☐ Non targeted/unknown (e.g., chart review) ☑ Other

If chart reviews will be used to identify potential subjects that are not your own patients, request a partial waiver of HIPAA Authorization for the purpose of identifying individuals for recruitment.

Describe.

Participants will be recruited by the principal investigator or Study Coordinator from the inpatient CF population at UAB. Dr. Amit Gaggar is a UAB physician and part of the UAB CF Care team. He is a Sub Investigator on this project and will assist in recruiting patients.

*Describe participant inclusion/exclusion criteria, including sex, race/ethnicity, age, and health status.

Inclusion criteria will include diagnosis of CF, age > 19 years, colonization with Pseudomonas Aeruginosa, and acute pulmonary exacerbation requiring inpatient care or out-patients .

Exclusion criteria include concurrent or recent (within 28 days of enrollment) use of corticosteroids, acute respiratory failure requiring the use of invasive or noninvasive ventilation, chronic liver or renal disease, and pregnancy

Describe the esĀmated Āme commitment of each subject. Examples: 1) One hour once a week for 52 consecutive weeks; 2) Twenty minutes to complete a one-time survey; 3) One interview lasting 60 minutes. Enter "N/A" if participants are not directly involved.

The participant involvement will include 2 visits over 7 days of data collection

☐ Yes ☑ No * Will a Certificate of Confidentiality be obtained from the NIH?

What recruitment materials/methods will be used to recruit subjects. Select all that apply.

☑ Flyer

Where will the flyer be distributed?
UAB CF Clinic

☐ Internet posĀng/website

☐ ResearchMatch

☐ Subject pool/repository

☐ Printed brochure

☐ Letter to healthcare providers

☐ Letter to potential subjects

☐ Printed ad

☐ Radio/TV ad

☐ Email solicitations

☑ Direct subject contact

Describe the methods used to recruit the subject (i.e., how, when). If participants without an exisĀng relationship with study personnel will be recruited via telephone, provide a copy of the required “Phone Script Template for Recruitment of Patients from an Electronic Health Record” and complete the IRB Training - Telephone Recruitment for Human Subject Research Participants course.

Participants will be recruited by the principal investigator or Study Coordinator from the inpatient and outpateint CF population at UAB. Dr. Amit Gaggar is a UAB physician and part of the UAB CF Care team. He is a Sub Investigator on this project and will assist in recruiting patients. Upon admission, Dr. Gaggar will alert the research team of the admission and a member of the research team will contact the patient to assess interest.

☐ Electronic Medical Record query using i2b2, Electronic Data Warehouse, or IMPACT

☐ Other

*Describe all activiĀes to idenĀfy and recruit prospecĀve parĀcipants.

(For assistance with the development of a Recruitment Plan, please contact CRSP.)

Select the types of data collecĀon tools that will be used in this study. Select all that apply.

☑ Survey/questionnaire(s) (UAB recommends using Qualtrics or RedCap for electronic surveys)

☐ Audio or video recordings

☐ Interview guides/scripts

☐ Subject diaries

☐ Mobile or web application

☐ Electronic Medical Record query using i2b2, Electronic Data Warehouse, or IMPACT

☐ Other

ProspecĀve Biospecimens

What type of biospecimens will be collected? Select all that apply. NOTE: If blood will be taken for screening and/or enrollment purposes, indicate them specifically. AddiĀonally, multiple specimens taken from the same person should be counted individually (e.g., 3 parĀcipants with 4 blood draws per participant equals 12 specimens).

☐ Tissue

☐ Bone marrow aspirates

☑ Blood

How many times will blood be collected? 2 Number of biospecimens. 2

Volume of blood per draw.
5-8 ml

Describe the blood collecĀon to include when, how oĀen, how, and volume (in teaspoons and milliliters).

additional blood will be collected at baseline and at visit 2 s for inpatients . This will be a single draw of 5-8 ml at two timepoints.

For outpaĀents blood will be collected at visit 1 and visit 2

☐ Fecal

☐ Semen

☑ Urine Number of biospecimens. 1

☐ Biopsy

☑ Other

Specify. Include number of biospecimens. NOTE: If mulĀple types specimens (e.g., blood, urine, etc.) are obtained from the same person, they count as one.

If the patient can expectorate additional sputum will be collected at visit 1 and visit 2

How will biospecimens be obtained, processed, distributed, and stored?

Blood samples will be collected from parĀcipants aĀer signing informed consnet. Sampes will be stored and processed in Dr. Plaisance's laboratory (Shelby Hall, 876A) for subsequent analysis.

How will biospecimens be labeled (e.g., unique idenĀfier, medical record number, social security number, name, date of birth)?

Specimens will be labeled with a parĀcipant code and the date of the sample. The parĀcipant code will be a randomly assigned, unique alphanumeric idenĀfier

How will clinical data associated with the biospecimens be collected and stored?

Clinical data will be collected and stored using the same alphanumeric identifier as described above and will be entered into a secure database maintained on a firewall- and password-protected network drive

What participant identifying information will be collected and linked to the biospecimens?

Samples will be labeled with a participant code and the date of the sample. Information which would reveal the idenĀty of a participant code number or link data to an individual will be extremely limited.

What steps will be taken to maximize the confidentiality of linked identifiers? For example, procedures could include using a password-protected computer database to link identifiers, with limited personnel knowledgeable of the password, or coded identifiers released without the ability to link to clinical data (also called "stripped" or "anonymized" biospecimens).

ConfidenĀality of all parĀcipants will be fully protected and invesĀgators will only use unique idenĀficaĀon numbers for labeling study samples and for compiling data files. Access to parĀcipant data will be strictly limited under control of the PI. Any publicaĀon of these data will not idenĀfy the participant by name.

Describe how the above numbers were determined (e.g., provide a power analysis, explain the pilot data, or reference prior studies.

Allocation of participants in a 2:1 (ketone:placebo control) fashion in blocks of 3 was chosen because this is a pilot study designed to provide preliminary data for an extramural grant. Descriptive statistics will be calculated for all quantitative measures, including assessments of acceptability and tolerability. We will have the appropriate number of patients available to address our questions.

Where are the specimens coming from (i.e., from the participant, repository, etc.)?

the parĀcipant

Indicate UAB's role. Select all that apply.

☐ Serving as central laboratory ☐ Central biospecimen repository ☐ Other

☐ Yes ☑ No * Will any genetic analyses be performed on the biospecimens?

☐ Yes ☑ No * Will the biospecimens include remnant material from a clinical procedure that would otherwise be discarded?

☐ Yes ☑ No * Will the biospecimens include extra material that would NOT have been taken for clinical purposes?

☑ Yes ☐ No * Are the biospecimens linked during the storage process, a er processing?

☐ Yes ☑ No * Could the study yield clinically relevant information?

☑ Yes ☐ No * Will the biospecimens be stored for future research?

What type of study is to be done with the biospecimens?

bio-specicems will be stored and distributed for the study of lung disease only a er verification of appropriate approval are in place

Describe how and where biospecimens will be stored. NOTE: If biospecimens will be stored in a BVAMC location, describe what IRB is responsible for overseeing the operaĀons of the biospecimen bank (i.e., local IRB or other mulĀ-site or central IRB?).

Sampes will be stored and processed in Dr. Plaisance's laboratory (Shelby Hall, 876A) for subsequent analysis.

Describe how the privacy of subject and the confidentiality of data will be protected.

A master subject log will be maintained by the PI. The Log will be maintained on a UAB encrypted computer which are password protected

Who will have access to the biospecimens, including the requirements for access, and who has control of this access?

Only Dr. Plaisance and his team will have access to the database and the samples. Only Dr. Plaisance will oversee distribution and he is responsible to ensure that all IRB approvals are in place before distributing any samples for future research

Describe the procedures in place for subjects to withdraw their biospecimens or whether deidentification makes subject withdrawal impossible.

Should the participant wish to withdraw their consent or specimen they can reach out to Dr. Plaisance . His contact information is provided in the Informed consent.

☑ Yes ☐ No * Is the banking of the biospecimens opĀonal?

Include in the consent the applicable sections of the Storage for Future Use language.

☐ Yes ☑ No Will biospecimens be shared with other investigators in the future?

☐ Yes ☑ No * Will the biospecimens be stored indefinitely?

Describe the methods that will be used to discard specimens at the end of the study life cycle.

A er analysis for protocol described outcomes the samples will be banked and stored for future research if the particpant consents. If not they will be destroyed

☑ Yes ☐ No Will specimens be used and/or shared for commercial profit?

☐ Yes ☑ No Will participants be informed of the results of the specimen tesĀng?

☐ Yes ☑ No Are there any implications for family members based on specimen testing results?

Clinical Trials

* Select whether this protocol meet the definiĀon of a clinical trial. ◉ Clinical Trial ○ Non-clinical trial

This protocol must be registered on clinicaltrials.gov. Provide the National Clinical Trial (NCT) idenĀfier. NCT04938726

NCT identifiers are **required** for IRB approval of a clinical trial; however, if all other information is complete and accurate, pending NCT identifiers can be obtained in parallel with the IRB's review of the submission.

All key personnel must complete Good Clinical Practices (GCP) training.

Institutional Biosafety Committee (IBC)

☐ Yes ☑ No * Does this project involve gene transfer, recombinant DNA, or CAR T cells?

11. LOCATIONS

☑ UAB Hospital

☐ The Kirklin Clinic of UAB Hospital

☐ UAB Callahan Eye Hospital

☑ Children's of Alabama (CoA)

☐ Jefferson County Department of Health (JCDH)

☐ UAB Hospital - Highlands

☐ The Kirklin Clinic at Acton Road

☐ UAB Clinical Research Unit

☐ Jefferson County Department of Health (JCDH)

☐ Other (i.e., any performance site not listed above, including those covered by subawards related to this protocol)

☐ Yes ☑ No * Is this a field study?

12. DEVICES

☐ Comparison

☑ Randomized

☐ Open Label

☐ Control

☐ Other

☑ Yes ☐ No * Is the trial blinded?

* Is the trial single or double blinded? Double Blinded

13. DEVICE SELECTION

Add a Device Review Sheet for each device the study involves.

Device Name	Device Review Sheet
Keto Mojo	DEVICE REVIEW SHEET Complete

14. DRUGS

Drugs, Biologics, and Supplements

What phase is the project? NOTE: If the drug is not being studied directly (i.e., an anxiolytic given to reduce anxiety before an MRI), state "Drug is not being studied directly."

proof of concept pilot trial

☐ Yes ☑ No * Will this study involve the use of radioisotopes managed by the UAB Radiopharmacy?

15. DRUG SELECTION

Add a Drug Review Sheet for each drug the study involves.

Drug Name	Drug Review Sheet
Ketone ester	DRUG REVIEW SHEET Complete

18. PATIENTS

☑ Yes ☐ No * Will the investigators (any investigator listed as key personnel) be recruiting their own patients?

Provide the rationale for including patients of investigators.

Participants will be recruited by the principal investigator or Study Coordinator from the inpatient and outpatient CF population at UAB . Dr. Amit Gaggar is a UAB physician and part of the UAB CF Care team. He is a Sub Investigator on this project

What safeguards are in place to ensure that investigators are not unduly coercing their patients into participation?

Patients will be consented by trained study team members and will not be pressured. Voluntary participation will be emphasized to all participants

25. COST AND PAYMENT

Cost, Reimbursement, or Compensation

☐ Yes ☑ No * Will subjects (or their insurance providers) experience costs associated with any of the procedures, drugs, biologics, devices, tests, or any aspect of their parĀcipaĀon in the study?

☑ Yes ☐ No * Will subjects receive any reimbursement or compensation for their participation (compensation should not be an amount that could be considered coercive or create undue influence)?

Select whether parĀcipants will receive payment and/or reimbursement.

☑ Payment

Provide the payment details, including amount, frequency of payment (e.g., $20 at visits one, two, and three), and the method of payment (e.g., cash, check, direct deposit, etc.).

The participant will receive $300.00. We will use the UAB greenphire system or checks to deliver the study payment.

NOTE: If subjects are being paid for their participation (not reimbursed for study-related expenses) in an amount of $600 or more in a single calendar year, their information will be reported to the IRS in accordance with federal requirements. This must be clearly stated in the informed consent form.

☐ Reimbursement

26. RISKS

Risks and Risk MinimizaĀon

Determine any anticipated risks or potential discomforts experienced by subjects for this study. Select all that apply.

☑ Physical risks (e.g., pain, bruising, and infection associated with venipuncture, adverse reactions to drugs, muscle soreness and pain as a consequence of exercise testing, heart attack induced by maximal exercise test, radiation risk (e.g., x-ray, CT scan, radiation therapy, radioisotopes, fluoroscopy))

Provide details of the risks, including expected frequency and severity.

Participants may experience some side effects from taking the study supplement. This includes gastrointestinal distress such bloating, belching, or nausea. These side effects are usually mild and may only last up to a few hours.

Describe any steps taken to mitigate the expected risks.

The described side effects are mild in nature and do not present any health concerns. However if a patient should experience concerning discomfort they will be evaluated by the study doctor.

☐ Psychological risks (e.g., depression and confusion as a result of administration of drugs, feelings of guilt precipitated by a sensitive survey)

☐ Social risks (e.g., invasion of privacy, breach of confidentiality, loss of community standing)

☐ Economic risks (e.g., loss of employment, loss of potenĀal monetary gain)

☐ Other risks

Indicate how safety is being monitored in this study.

☐ Data Safety Monitoring Board (DSMB)

☐ Independent medical monitor

☑ Data will be monitored by PI.

Describe how safety will be monitored locally and, if this is a multi-center study, how data and safety will be monitored across sites. Additionally, describe how oĀen data will be monitored. If the only risk is breach of confidentiality, descrbe the method of monitoring for breaches.

The study PI will evaluate all adverse events from each enrolled participant as they occur in order to ensure subject safety.

☐ Data will not be monitored.

27. BENEFITS

Describe.

The participant may or may not experience benefits from participating. The potential benefits include a reduction of inflammation in the lungs and blood which could improve health outcomes for the participant.

What are the potenĀal benefit(s) of the study (e.g., benefits to society, increased knowledge of the parĀcular disease, increased scienĀfic knowledge, etc.)?

The potential benefits include a reduction of inflammation in the lungs and blood which could improve health outcomes for the parĀcipant.

28. PRIVACY AND CONFIDENTIALITY

Select the identifiers.

☑ Names

☐ All geographical subdivisions smaller than a state, including street address, city, county, precinct, zip code, and their equivalent geocodes, except for the initial three digits of a zip code, if according to the current publicly available data from the Bureau of the Census: (1) The geographic unit formed by combining all zip codes with the same three iniĀal digits contains more than 20,000 people; and (2) The iniĀal three digits of a zip code for all such geographic units containing 20,000 or fewer people is changed to 000

☑ All elements of dates (except year) for dates directly related to an individual, including birth date, admission date, discharge date, date of death; and all ages over 89 and all elements of dates (including year) indicative of such age, except that such ages and elements may be aggregated into a single category of age 90 or older

☐ Phone Numbers

☐ Fax Numbers

☐ Email Addresses

☐ Social Security Numbers

☑ Medical Record Numbers

☐ Health plan beneficiary numbers

☐ Account numbers

☐ Certificate/license numbers

☐ Vehicle identifiers and serial numbers, including license plate numbers

☐ Device identifiers and serial numbers

☐ Web universal resource locators (URLs)

☐ Internet protocol (IP) addresses

☐ Biometric idenĀfiers, including finger and voice prints

☐ Full face photographic images and any comparable images

☐ Any other unique idenĀfying number, characteristic, or code

☑ Medical history

☐ Surgical history

☑ Laboratory results

☐ Other

Provide the length of time the identifiers will be stored or retained.

one year past study close out.

Describe how data will be collected, recorded, and shared, including the specific safeguards to protect the confidentiality of data. Select all that apply.

☐ Working with an entity outside of UAB to collect, record, share, or otherwise utilize the data.

☐ Data will be stored in REDCap.

☐ Data will be stored in ShareFile

☐ Data will be kept on a UAB encrypted device (i.e., computer, tablet, etc.).

☑ Data will be stored on a UAB encrypted server.

☐ Data will be stored in the UAB Cheaha Supercomputer

☐ Data will be recorded on paper.

☑ Data will be coded.

☑ Yes ☐ No * Will a key to the code be maintained?

Who will have access to the key?
THe PI

☐ Data will be kept in a locked office/filing cabinet.

☐ Data will be stored on a password protected computer/drive not maintained by UAB.

☐ Data will be stored in a location not described above.

☐ Data will NOT be coded.

Describe the plan to destroy the subject identifiers at the earliest opportunity consistent with the conduct of research, unless retention is required for reasons of health, research, or law (including the methods that will be used to discard data at the end of the study life cycle). NOTE: Research records must be retained and subsequently discarded in accordance with applicable regulatory guidelines.

HIPAA Authorization

Indicate whether you will obtain HIPAA Authorization, a HIPAA waiver, whether the data meet the specifications for a Limited Data Set, or whether the study does not involve access, review, or disclosure of Protected Health Information (PHI). Select all that apply.

☐ Request for partial HIPAA waiver for recruitment/screening purposes.

☑ HIPAA AuthorizaÃon will be obtained for some or all of the subjects.

NOTE: Ensure the appropriate HIPAA authorization language has been added to the consent form.

All * Will HIPAA authorizaÃon be obtained from all or some of the subjects?

☑ Yes ☐ No * Will the study team ensure HIPAA authorization is obtained in a private setting?

☐ Request for HIPAA waiver for some or all of the subjects (e.g., for retrospective review of PHI, and/or to review PHI for recruitment purposes and obtain HIPAA authorization during enrollment)

☐ The data meet the specifications for a limited data set. NOTE: A limited data set will only apply if you receive data from an outside source as a limited data set or if you are sending data to an outside source as a limited data set (in which case, documentation of authorization or a Waiver of Authorization will be required). A Data Use Agreement (DUA) is required for this option.

HIPAA Covered Entities

Indicate which of the entities would provide health information for this protocol, maintain health information as it was collected for this protocol, and/or store health information a er it has been collected for this protocol.

☑ UAB Hospital or UAB Hospital - Highlands

☐ The Kirklin Clinic of UAB Hospital or Acton Road (and/or associated clinics)

☐ UAB Callahan Eye Hospital

☐ Children's of Alabama

☐ Jefferson County Department of Health

☐ School of DenÃstry

☐ School of Health Professions

☐ School of Medicine

☐ School of Nursing

☐ School of Optometry

☐ University of Alabama Health Services FoundaÃon

☐ Valley Foundation

☐ Medical West - UAB Health System Affiliate

☐ Birmingham Veteran's Affairs Medical Center

☐ Yes ☑ No Is the principal investigator requesting that the UAB IRB waive patient HIPAA authorization from another institution or entity (e.g., insurance company, collaborating institution)?

29. CONSENT

Informed Consent

Indicate all that apply to the informed consent process.

☑ Informed consent with written documentation will be obtained from all or some of the subjects.

Select all types of consent forms that will be used.

Consent Form Types	Description of Document (50 words or less)	Clean Copy	Tracked Copy

All * Will written informed consent be obtained from all or some of the subjects?

Describe how written informed consent will be obtained, including confirmaÃon that a copy of the signed consent document will be given to the individual who will sign it.

Consent will be obtained in a private setting by trained research staff and a signed copy will be provided to the participant.

Describe how the study team will ensure the subjects understand the information presented.

The team will ask frequent questions to the participant during the consent process to ensure they understand

What language will the prospective participant understand?

English

What language will be used to obtain consent?

English

☐ Yes ☑ No Will any potential participants be, or have been, in a stressful, painful, or drugged condition before or during the consent process?

☐ Request a Waiver of Documentation of Informed Consent (e.g., subject may not sign an informed consent document, but will be given an information sheet)

☐ Request a Waiver or Alteration of some or all elements of informed consent or a FULL waiver of informed consent.

31. ATTACHMENTS

Attachments

Document Name	Document Type	DescripĀon of Document (50 words or less)	Clean Copy	Tracked Copy	
Protocol Oversight Review Form	IRB Submission Form				
Data Collection Sheet	Data Collection				
Response Memorandum	Other				
Response Memorandum	Other				
Survey/Questionnaire	Other	CFQR			
Survey/Questionnaire	Other	symptom questionnaire			
Survey/Questionnaire	Other	Food Diary			
Flyer	Other	flyer			
DSMB Charter	Other	DSMP plan			

Updated By: Eric P. Plaisance @ 24-Sep-2024 12:26:21 PM

UAB INTEGRATED RESEARCH ADMINISTRATION PORTAL

Device Review Sheet

DEVICE SELECTION

Devices

Device Name Keto Mojo

☐ Yes ☑ No Is an Investigational Device Exemption (IDE) required?

☑ Yes ☐ No IDE Exempt

Select the applicable IDE Exempt categor(ies).

☑ Category 1: A legally marketed device when used in accordance with its labeling.

Provide justification for the device meeting this category

This meter is commercially available without a prescription

☐ Category 2: A diagnostic device if it complies with the labeling requirements in §809.10(c) and if the tesĀng: a) is noninvasive; b) does not require an invasive sampling proedure that presents significant risk; c) does not by design or intention introduce energy into a subject; and d) is not used as a diagnostic procedure without confirmation by another medically established diagnostic product or procedure. Additional guidance for in vitro diagnostic device studies can be found here.

☐ Category 3: Consumer preference testing, testing of a modification, or testing of a combination of devices if the device(s) are legally marketed device(s) [that is, the devices have an approved PMA, cleared Premarket Notification 510(k), or are exempt from 510(k)] AND if the testing is not for the purpose of determining safety or effectiveness and does not put subjects at risk.

☐ Category 4: A device intended solely for veterinary use.

☐ Category 5: A device shipped solely for research with laboratory animals and contains the labeling "CAUTION – Device for investigational use in laboratory animals or other tests that do not involve human subjects.

☐ Yes ☑ No Is the device a Humanitarian Use Device (HUD)?

☐ Yes ☑ No Has the FDA made a device study determination?

Submit any applicable documentation from the FDA.

DescripĀon	Document	

☐ Yes ☑ No Are you requesting the IRB make a Nonsignificant Risk determination for this device?

Describe the plan for the storage, dispensing, and disposal of the device being studied. Note: If the device is not FDA-approved, the plan must include methods to segregate the investigational devices from other devices available for general use.

The ketone meter is multi use and will be kept by the research coordinator, this devise is not given out to patients

Describe how safety will be monitored for this device.

There is no safety monitoring for this device

Refer to the following FDA guidances for helpful information and examples.

1) Frequently Asked Questions About Medical Devices
2) Significant Risk and Nonsignificant Risk Medical Device Studies
3) In Vitro Diagnostic Device (IVD) Studies - Frequently Asked Questions

Updated By: Eric P. Plaisance @ 24-Sep-2024 12:26:21 PM

University of Alabama at Birmingham

Office of the IRB

Phone: 205-934-3789 | Fax: 205-934-1301

www.uab.edu/irb

Questions?

Form Version: 2.0 | Date: 01/04/2021

UAB INTEGRATED RESEARCH ADMINISTRATION PORTAL

Drug Review Sheet

DRUG SELECTION

Drugs

Drug name exogenous ketone ester

☐ Yes ☑ No Is an Investigational New Drug Application (IND) required?

☐ Yes ☑ No Has the requirement for an IND been waived?

☐ Yes ☑ No Has the drug received FDA Approval?

Provide the name of the person holding the IND.

NA This a supplement and does not require FDA approval

Submit a copy of the Release of Drugs for Human Research Use (UAB Pharmacy (FOR 217), Children's of Alabama (FOR 218).

From where will the drugs be obtained?

A company called Ketone Aid will provide the blinded supplement or placebo. The inpatient participants will receive the ketone supplement and placebo from the pharmacy but the outpatient participants will receive the ketone supplement and placebo from the research staff.

☐ Yes ☑ No Do you have an investigator's brochure available?

Describe the plan for the storage, dispensing, and disposal of the drug(s)/biologic(s).

For the outpatient parĀcipants, the PI will store, monitor and dispense the blinded product to the research staff for dispensing to the patient per the randomization code. The PI will maintain a product accountability log.
For the inpaĀent parĀcipants, the research pharmacy will store and dispense the supplement to the parĀcipant. The research pharmacy will maintain a product accountability log for the inpatients.

☐ Yes ☑ No Is this a combination therapy (e.g. an investigational product in combination with commercially approved agent(s), two or more commercially approved agents are being combined, etc.)?

Describe the route of administration.

oral

☑ Yes ☐ No Is the drug commercially available?

The drug will be used for: A new indication, new population, new route of administration, or new dosage

Explain.

Evidence exist that ketone supplement decrease systemic inflammation

Describe how safety will be monitored for this drug.

Adverse Events will be monitored throughout the course of the study and the team will meet weekly to discuss patient safety

Updated By: Eric P. Plaisance @ 24-Sep-2024 12:26:21 PM

Appendix 1

EForm Name: IRB EPORTFOLIO
Page: 31. ATTACHMENTS
Section:
Question: Clean Copy
File Name: PORF_210614.docx

THE UNIVERSITY OF ALABAMA AT BIRMINGHAM

Institutional Review Board

Protocol Oversight Review Form

Date Submitted to IRB: **06/14/2021**

Title of Project: **Ketone monoester supplementation in cystic fibrosis: A pilot and feasibility study**

Name of Principal Investigator: **Eric P. Plaisance**

Signature of Principal Investigator: Eric P. Plaisance

School: **University of Alabama at Birmingham**
Department: **Human Studies**
Division: **School of Education**

Review Process (as determined by Department Chair or Dean):

- ☒ School Review
- ☐ Divisional Review (Division Director or Designate)
- ☐ Center or Departmental Protocol Review Committee Review
- ☐ Project Review Panel (PRP)—Appointed by the Department Chairman or Division Director (PRP report attached)

I have reviewed the proposed research and concluded that the following apply:

- The research is scientifically valid and is likely to answer the scientific question;
- The researcher and the study team are qualified and/or credentialed to conduct the procedures proposed;
- The researcher has identified sufficient resources in terms of experienced research personnel, facilities, and availability of medical or psychological services that may be necessary as a consequence of participation in the research to protect the research participants.

Name of Official: **Dr. Michelle Robinson** Title: **Interim Dean**
(type or print)

Signature: Michelle Robinson Date: 06/10/21

SCHOOL OF EDUCATION
Human Studies

1150 10th Ave S
BIRMINGHAM AL 35294-0110

phone: 205.996.7909
www.uab.edu

Appendix 2

EForm Name: IRB EPORTFOLIO
Page: 31. ATTACHMENTS
Section:
Question: Clean Copy
File Name: DATA SHEET.210614.doc

Pre / Post Assessment (Circle)	*Physiological Data Sheet*

PARTICIPANT INFORMATION

Name	ID	Today's Date
		/ /

Sex	Age	Height	Weight
	yrs	inches	lbs

Medications "On Board" / Special Precautions

KETONE CONCENTRATIONS			
Time	**BHB**	**Glucose**	**Comments**
0			
15			
30			
60			
90			
120			

PULMONARY FUNCTION TESTING		
Time		**Comments**
FEV_1		
FVC		
FEV_1/FVC		

Notes:

Appendix 3

EForm Name: IRB EPORTFOLIO
Page: 31. ATTACHMENTS
Section:
Question: Clean Copy
File Name: response.210827.doc

THE UNIVERSITY OF ALABAMA AT BIRMINGHAM
Office of the Institutional Review Board for Human Use

470 Administration Building
701 20th Street South
Birmingham, AL 35294-0104
205.934.3789 | Fax 205.934.1301 | irb@uab.edu

DETERMINATION LETTER

TO: Plaisance, Eric P.

FROM: University of Alabama at Birmingham Institutional Review Board
Federalwide Assurance # FWA00005960
IORG Registration # IRB00000196 (IRB 01)
IORG Registration # IRB00000726 (IRB 02)
IORG Registration # IRB00012550 (IRB 03)

DATE: 25-Aug-2021

RE: IRB-300007323
Ketone Monoester Supplementation in Cystic Fibrosis: A Pilot and Feasibility Study

---

The IRB reviewed the Initial Application submitted on 05-Aug-2021 for the above referenced project. The review was conducted in accordance with UAB's Assurance of Compliance approved by the Department of Health and Human Services.

Type of Review: Full - Institutional Review Board 02 (UAB)
Determination: Additional information required
Determination Date: 18-Aug-2021

Please respond to the items listed below. The response must be submitted through IRAP. Visit the IRAP page on the UAB IRB website for guidance on responding through IRAP. Click on "How to Respond to an IRB Request for Changes".

Items to Address:

1. All key personnel involved in the research must complete the initial IRB training (4 credit requirement), then continuing IRB training (refresher) every 3 years. Please check the IRB web site at **https://www.uab.edu/research/home/irb-training-page** for more information.

   The following individuals must complete **continuing IRB training:**

   - *Amit Gaggar*

2. Make sure the e-Personnel Form includes all research staff that will be working on this study including Amit Gaggar and Respiratory Therapists. Amit Gaggar has been removed from the protocol and will be added when he completes his training. All respiratory therapist and everyone else on the IRB has current training.

The following pertains to the e-Portfolio:

3. SECTION 1 GENERAL QUESTIONS, Background

    a. Add a description of what will be analyzed in the blood (5-8mls) and sputum for research purposes. Mentioning biomarkers of inflammation will suffice. added

The following pertains to the consent form:

4. In the **Purpose of the Research Study**, add a description of what will be analyzed in the blood (5-8mls) and sputum for research purposes. Mentioning biomarkers of inflammation will suffice. added

5. In the bullets for Sputum and Blood Collection in the **Study Participation & Procedures** section, it states that each of these biospecimens will be collected for research twice (during days 1-3 and 5-7). The IRB thinks this may be confusing for participants. Revise the section to state collection will take place once on day 1, 2, or 3, and then another sample collected on days 5, 6, or 7. done

6. In the **Information for Women of Childbearing Potential, Nursing Mothers, and/or Men Capable of Fathering a Child** section, remove the third paragraph since the study agent (ketones) is expected to be cleared from their systems within a few hours after ingestion. This appears to have been a "cut and paste" error from another consent document. done

7. In the third sentence of the **Payment for Participation** section, revise the sentence to the following: "The total payment you will receive is $300.00." done

The IRB or designated reviewer must review your response submission before you receive formal IRB approval. No activity related to this project may occur until the Office of the IRB issues the IRB Approval Letter and, if applicable, any IRB-stamped consent forms.

RESPONDING TO COMMENTS FROM THE OIRB IN IRAP
ONLY RESPOND WHEN ALL ITEMS ARE COMPLETE, INCLUDING OUTSTANDING TRAINING

- Navigate to the project record in IRAP and open the record.
- The project will open to the Submissions folder. The submission for which revisions are required will have a blue "Respond" hyperlink. Click that link to create a Response submission.
- After clicking Respond, a new window will open. Click the drop down, in which the only option will be Response to Info/Mod Request. Choose Response to Info/Mod Request and click Save.
- The Response submission will then be created, which will include a copy of the previously completed IRB ePortfolio.
- Generate your response memo
    - Save this document as "response.yymmdd"
    - Type in your response in the designated areas using the formatting provided (bold text, italics).
    - Use full sentences and responses; avoid "completed", especially when addressing the question differently than requested, when questions are asked or clarity is needed.

    - If adding any additional changes that were not requested, add them to the end of your response memo by inserting a new row and using bold and italics for your response.
    - **Upload this file with the other revised documents in the applicable sections of the IRB ePortfolio**
    - NOTE: Failure to provide a response memo may result in a delay in your project and an additional request for its provision.
- Make any requested changes to the IRB ePortfolio.
- **Replace attachments that require revisions.**
- Revise the needed documents or gather missing documents:
    - **Use MSOffice's tracked changes functionality**.
    - Submit both a tracked version of the document and a clean version. NOTE: Failure to provide a tracked version may result in a delay in your project and an additional request for its provision.
    - Save the revised file by changing the YYMMDD suffix and adding ".tracked" or ".clean" to any document changed.
    - Do not save files as PDFs. PDFs should only be submitted when the document requires a signature or is not available in its native format. All clean and tracked versions should be submitted in the format in which they were created if at all possible.
    - Upload the newly revised documents.

Appendix 4

EForm Name: IRB EPORTFOLIO
Page: 31. ATTACHMENTS
Section:
Question: Clean Copy
File Name: response.210831.doc

THE UNIVERSITY OF ALABAMA AT BIRMINGHAM
Office of the Institutional Review Board for Human Use

470 Administration Building
701 20th Street South
Birmingham, AL 35294-0104
205.934.3789 | Fax 205.934.1301 | irb@uab.edu

ADMINISTRATIVE PRE-REVIEW

TO: Plaisance, Eric P.

FROM: University of Alabama at Birmingham Institutional Review Board
Federalwide Assurance # FWA00005960
IORG Registration # IRB00000196 (IRB 01)
IORG Registration # IRB00000726 (IRB 02)
IORG Registration # IRB00012550 (IRB 03)

DATE: 30-Aug-2021

RE: IRB-300007323
Ketone Monoester Supplementation in Cystic Fibrosis: A Pilot and Feasibility Study

---

The Office of the IRB staff has completed the administrative pre-review of the Response to Info/Mod Request submitted on 27-Aug-2021 for the above referenced project. Please respond to the items listed below. The response must be submitted through IRAP.

Visit the IRAP page on the UAB IRB website for guidance on responding through IRAP. Click on the "Quick Step by Step Instructions for How to Respond to an IRB Review".

Due to Dr. Gaggar's role in the study, we cannot issue formal approval until his training is completed. Once his training is completed, revise the Personnel eForm and attach a copy of his training where indicated (training certificate) section of the Personnel eForm. Also include the degrees for each person listed. Dr. Gaggar has been added and his training certificate has been uploaded. All degrees have been added as well. Thanks!

Let me know if you have any questions.

Thanks,

Margie Lawson (mlawson@uab.edu)

Appendix 5

EForm Name: IRB EPORTFOLIO
Page: 31. ATTACHMENTS
Section:
Question: Clean Copy
File Name: Queastionaire(CFQR).220110.pdf

Section II. Quality of Life

Please check the box indicating your answer.

*During the past **two weeks**, to what extent have you had difficulty:*	**A lot of difficulty**	**Some difficulty**	**A little difficulty**	**No difficulty**
1. Performing vigorous activities such as running or playing sports	☐	☐	☐	☐
2. Walking as fast as others	☐	☐	☐	☐
3. Carrying or lifting heavy things such as books, groceries, or school bags	☐	☐	☐	☐
4. Climbing one flight of stairs	☐	☐	☐	☐
5. Climbing stairs as fast as others	☐	☐	☐	☐

***During the past two weeks**, indicate how often:*	**Always**	**Often**	**Sometimes**	**Never**
6. You felt well	☐	☐	☐	☐
7. You felt worried	☐	☐	☐	☐
8. You felt useless	☐	☐	☐	☐
9. You felt tired	☐	☐	☐	☐
10. You felt energetic	☐	☐	☐	☐
11. You felt exhausted	☐	☐	☐	☐
12. You felt sad	☐	☐	☐	☐

Please circle the number indicating your answer. Please choose only one answer for each question.

*Thinking about the state of your health over the last **two weeks**:*

13. To what extent do you have difficulty walking?
1. You can walk a long time without getting tired
2. You can walk a long time but you get tired
3. You cannot walk a long time because you get tired quickly
4. You avoid walking whenever possible because it's too tiring for you

14. How do you feel about eating?
1. Just thinking about food makes you feel sick
2. You never enjoy eating
3. You are sometimes able to enjoy eating
4. You are always able to enjoy eating

15. To what extent do your treatments make your daily life more difficult?
1. Not at all
2. A little
3. Moderately
4. A lot

16. How much time do you currently spend each day on your treatments?
1. A lot
2. Some
3. A little
4. Not very much

17. How difficult is it for you to do your treatments (including medications) each day?
1. Not at all
2. A little
3. Moderately
4. Very

18. How do you think your health is now?
1. Excellent
2. Good
3. Fair
4. Poor

Please select a box indicating your answer.

*Thinking about your health during the past **two weeks**, indicate the extent to which each sentence is true or false for you.*	Very true	Somewhat true	Somewhat false	Very false
19. I have trouble recovering after physical effort	☐	☐	☐	☐
20. I have to limit vigorous activities such as running or playing sports	☐	☐	☐	☐
21. I have to force myself to eat	☐	☐	☐	☐
22. I have to stay at home more than I want to	☐	☐	☐	☐
23. I feel comfortable discussing my illness with others	☐	☐	☐	☐
24. I think I am too thin	☐	☐	☐	☐
25. I think I look different from others my age	☐	☐	☐	☐
26. I feel bad about my physical appearance	☐	☐	☐	☐
27. People are afraid that I may be contagious	☐	☐	☐	☐
28. I get together with my friends a lot	☐	☐	☐	☐
29. I think my coughing bothers others	☐	☐	☐	☐
30. I feel comfortable going out at night	☐	☐	☐	☐
31. I often feel lonely	☐	☐	☐	☐
32. I feel healthy	☐	☐	☐	☐
33. It is difficult to make plans for the future (for example, going to college, getting married, advancing in a job, etc.)	☐	☐	☐	☐
34. I lead a normal life	☐	☐	☐	☐

Section III. School, Work, or Daily Activities

Questions 35 through 38 are about school, work, or other daily tasks.

35. To what extent did you have trouble keeping up with your schoolwork, professional work, or other daily activities during the past **two weeks**?

1. You have had no trouble keeping up
2. You have managed to keep up but it's been difficult
3. You have been behind
4. You have not been able to do these activities at all

36. How often were you absent from school, work, or unable to complete daily activities during the last two weeks because of your illness or treatments?

☐ Always ☐ Often ☐ Sometimes ☐ Never

37. How often does CF get in the way of meeting your school, work, or personal goals

☐ Always ☐ Often ☐ Sometimes ☐ Never

38. How often does CF interfere with getting out of the house to run errands such as shopping or going to the bank?

☐ Always ☐ Often ☐ Sometimes ☐ Never

Section IV. Symptom Difficulties

Please select a box indicating your answer.

*Indicate how you have been feeling during the past **two weeks**.*	**A great deal**	**Somewhat**	**A little**	**Not at all**
39. Have you had trouble gaining weight?	☐	☐	☐	☐
40. Have you been congested?	☐	☐	☐	☐
41. Have you been coughing during the day?	☐	☐	☐	☐
42. Have you had to cough up mucus?	☐	☐	☐	☐ **Go to Question 44**

43. Has your mucus been mostly: ☐ Clear ☐ Clear to yellow ☐ Yellowish-green ☐ Green with traces of blood ☐ Don't know

*How often during the past **two weeks**:*	**Always**	**Often**	**Sometimes**	**Never**
44. Have you been wheezing?	☐	☐	☐	☐
45. Have you had trouble breathing?	☐	☐	☐	☐
46. Have you woken up during the night because you were coughing?	☐	☐	☐	☐
47. Have you had problems with gas?	☐	☐	☐	☐
48. Have you had diarrhea?	☐	☐	☐	☐
49. Have you had abdominal pain?	☐	☐	☐	☐
50. Have you had eating problems?	☐	☐	☐	☐

Please be sure you have answered all the questions.

THANK YOU FOR YOUR COOPERATION!

CFQ - R

Parents/Caregivers (Children Ages 6 to 13)

CYSTIC FIBROSIS QUESTIONNAIRE - REVISED

Understanding the impact of your child's illness and treatments on his or her everyday life can help your healthcare team keep track of your child's health and adjust his or her treatments. For this reason, we have developed a quality of life questionnaire specifically for parents of children with cystic fibrosis. We thank you for your willingness to complete this questionnaire.

Instructions: The following questions are about the current state of your child's health, as he or she perceives it. This information will allow us to better understand how he or she feels in everyday life.
Please answer all the questions. There are no right or wrong answers! If you are not sure how to answer, choose the response that seems closest to your child's situation.

Section I. Demographics

Please fill in the information or check the box indicating your answer.

A. What is your **child's** date of birth?

Date ☐☐ ☐☐ ☐☐☐☐
Mo Day Year

B. What is your relationship to the child?

- ☐ Mother
- ☐ Father
- ☐ Grandmother
- ☐ Grandfather
- ☐ Other relative
- ☐ Foster mother
- ☐ Foster father
- ☐ Other (please describe)

_____

C. Which of the following best describes your child's racial or ethnic background?

- ☐ Caucasian
- ☐ African American
- ☐ Hispanic
- ☐ Asian/Oriental or Pacific Islander
- ☐ Native American or Native Alaskan
- ☐ Other (please describe)

_____

- ☐ Prefer not to answer this question

D. During the **past two weeks**, has your child been on vacation or out of school for reasons **NOT** related to his or her health?

☐ Yes ☐ No

E. What is **your** date of birth?

Date ☐☐ ☐☐ ☐☐☐☐
Mo Day Year

F. What is your current marital status?

- ☐ Single/never married
- ☐ Married
- ☐ Widowed
- ☐ Divorced
- ☐ Separated
- ☐ Remarried
- ☐ With a partner

G. What is the highest grade in school you have completed?

- ☐ Some high school or less
- ☐ High school diploma/GED
- ☐ Vocational school
- ☐ Some college
- ☐ College degree
- ☐ Professional or graduate degree

H. Which of the following best describes you current work status?

- ☐ Seeking Work
- ☐ Working full or part time (either outside the home or at a home-based business)
- ☐ Full time homemaker
- ☐ Not working due to my health
- ☐ Not working for other reasons

Section II. Quality of Life

Please indicate how your child has been feeling during the past two weeks by checking the box matching your response.

To what extent has your child had difficulty:	**A lot of difficulty**	**Some difficulty**	**A little difficulty**	**No difficulty**
1. Performing vigorous activities such as running or playing sports	☐	☐	☐	☐
2. Walking as fast as others	☐	☐	☐	☐
3. Climbing stairs as fast as others	☐	☐	☐	☐
4. Carrying or lifting heavy objects such as books, a school bag, or backpack	☐	☐	☐	☐
5. Climbing several flights of stairs	☐	☐	☐	☐

Please check the box matching your response.

*During the past **two weeks**, indicate how often your child:*	**Always**	**Often**	**Sometimes**	**Never**
6. Seemed happy	☐	☐	☐	☐
7. Seemed worried	☐	☐	☐	☐
8. Seemed tired	☐	☐	☐	☐
9. Seemed short-tempered	☐	☐	☐	☐
10. Seemed well	☐	☐	☐	☐
11. Seemed grouchy	☐	☐	☐	☐
12. Seemed energetic	☐	☐	☐	☐
13. Was absent or late for school or other activities because of his/her illness or treatments	☐	☐	☐	☐

Please circle the number indicating your answer. Please choose only one answer for each question.

*Thinking about the state of your child's health over the past **two weeks**, indicate:*

14. The extent to which your child participated in sports and other physical activities, such as gym class
1. Has not participated in physical activities
2. Has participated less than usual in sports
3. Has participated as much as usual but with some difficulty
4. Has been able to participate in physical activities without any difficulty

15. The extent to which your child has difficulty walking
1. He or she can walk a long time without getting tired
2. He or she can walk a long time but gets tired
3. He or she cannot walk a long time, because he or she gets tired quickly
4. He or she avoids walking whenever possible, because it's too tiring for him or her

Please check the box that matches your response to these questions.

*Thinking about your child's state of health during the past **two weeks**, indicate the extent to which each sentence is true or false for your child:*

	Very true	Somewhat true	Somewhat false	Very false
16. My child has trouble recovering after physical effort	☐	☐	☐	☐
17. Mealtimes are a struggle	☐	☐	☐	☐
18. My child's treatments get in the way of his/her activities	☐	☐	☐	☐
19. My child feels small compared to other kids the same age	☐	☐	☐	☐
20. My child feels physically different from other kids the same age	☐	☐	☐	☐
21. My child thinks that he/she is too thin	☐	☐	☐	☐
22. My child feels healthy	☐	☐	☐	☐
23. My child tends to be withdrawn	☐	☐	☐	☐
24. My child leads a normal life	☐	☐	☐	☐
25. My child has less fun than usual	☐	☐	☐	☐
26. My child has trouble getting along with others	☐	☐	☐	☐
27. My child has trouble concentrating	☐	☐	☐	☐
28. My child is able to keep up with his/her school work or summer activities (e.g. camp)	☐	☐	☐	☐
29. My child is not doing as well as usual in school or summer activities (e.g. camp)	☐	☐	☐	☐
30. My child spends a lot of time on his/her treatments everyday	☐	☐	☐	☐

Please circle the number indicating your answer. Please choose only one answer for each question.

31. How difficult is it for your child to do his/her treatments (including medications) each day?
1. Not at all
2. A little
3. Moderately
4. Very

32. How do you think your child's health is now?
1. Excellent
2. Good
3. Fair
4. Poor

Section III. Symptom Difficulties

The next set of questions is designed to determine the frequency with which your child has certain respiratory difficulties, such as coughing or shortness of breath.

*Please indicate how your child has been feeling during the past **two weeks.***	**A great deal**	**Somewhat**	**A little**	**Not at all**
33. My child had trouble gaining weight	☐	☐	☐	☐
34. My child was congested	☐	☐	☐	☐
35. My child coughed during the day	☐	☐	☐	☐
36. My child had to cough up mucus	☐	☐	☐	☐ ↓ **Go to Question 38**

37. My child's mucus has been mostly: ☐ Clear ☐ Clear to yellow ☐ Yellowish-green ☐ Green with traces of blood ☐ Don't know

*During the past **two weeks:***	**Always**	**Often**	**Sometimes**	**Never**
38. My child wheezed	☐	☐	☐	☐
39. My child had trouble breathing	☐	☐	☐	☐
40. My child woke up during the night because he/she was coughing	☐	☐	☐	☐
41. My child had gas	☐	☐	☐	☐
42. My child had diarrhea	☐	☐	☐	☐
43. My child had abdominal pain	☐	☐	☐	☐
44. My child has had eating problems	☐	☐	☐	☐

Please be sure you have answered all the questions.

THANK YOU FOR YOUR COOPERATION!

Appendix 6

EForm Name: IRB EPORTFOLIO
Page: 31. ATTACHMENTS
Section:
Question: Clean Copy
File Name: queastionaire(symtom)220220.docx

ID CODE _____ Date _____

SYMPTOM QUESTIONNAIRE

How is your general health today? (Please check one box)

☐ Very Good ☐ Good ☐ Fair ☐ Poor

Please record any symptoms you may have had today (tick one box for each symptom experienced)

Absent *I did not have this symptom at all*
Mild *I had this symptom occasionally, but it didn't really bother me*
Moderate *I had this symptom often, it bothered me quite a bit*
Severe *I had this symptom very often, it bothered me a great deal*

	Absent	Mild	Moderate	Severe
Nausea	☐	☐	☐	☐
Vomiting	☐	☐	☐	☐
Heartburn	☐	☐	☐	☐
Stomach Pain	☐	☐	☐	☐
Diarrhea	☐	☐	☐	☐
Constipation	☐	☐	☐	☐
Bloating/Feeling of Fullness	☐	☐	☐	☐
Belching	☐	☐	☐	☐

If you experienced any of the above symptoms, at what point after supplementation did they occur?

	Immediately	One hour	Two hours	Three or more hours
Nausea	☐	☐	☐	☐
Vomiting	☐	☐	☐	☐
Heartburn	☐	☐	☐	☐
Stomach Pain	☐	☐	☐	☐
Diarrhea	☐	☐	☐	☐
Constipation	☐	☐	☐	☐
Bloating/Feeling of Fullness	☐	☐	☐	☐
Belching	☐	☐	☐	☐

ID CODE _____ Date _____

If you experienced any of the above symptoms, how long did they last? If applicable, please specify the number of times the symptom occurred.

	Less than 30 min	One hour	Two hours	Three or more hours
Nausea	☐	☐	☐	☐
Vomiting	☐	☐	☐	☐
Heartburn	☐	☐	☐	☐
Stomach Pain	☐	☐	☐	☐
Diarrhea	☐	☐	☐	☐
Constipation	☐	☐	☐	☐
Bloating/Feeling of Fullness	☐	☐	☐	☐
Belching	☐	☐	☐	☐

Final Day Question (only). Which study condition do you think you were in?

☐ Placebo condition (I **did not** drink the ketones)

☐ Ketone Condition (I did drink the ketones)

Additional Comments:

_____
_____
_____
_____
_____
_____
_____
_____
_____
_____
_____
_____

Appendix 7

EForm Name: IRB EPORTFOLIO
Page: 31. ATTACHMENTS
Section:
Question: Clean Copy
File Name: queastionaire (DAILY FOOD RECORD)220220.doc

Daily Food Record

- RECORD EVERYTHING YOU EAT AND DRINK INCLUDING SNACKS AND BEVERAGES.

- RECORD IMMEDIATELY AFTER FOOD IS CONSUMED

- INDICATE PORTION SIZES. MEASURE AMOUNTS OF EACH FOOD USING MEASURING CUPS OR SPOONS WHEN IT IS PRACTICAL. RECORD PORTION SIZES IN GRAMS, OUNCES, CUPS, TABLESPOONS, TEASPOONS, OR PIECES. (example: 8 oz. orange juice, 1 piece wheat bread, 1 tbsp. butter)

- INDICATE THE BRAND NAME. (3 oz. Ruffles BBQ Potato Chips, 1 cup Uncle Ben's Long Grain Rice, McDonald's Large French Fries)

- INDICATE FORM OF PURCHASE. (fresh, frozen, canned, etc.)

- RECORD TIME OF DAY MEAL WAS EATEN

- RECORD AND CHECK THE NUMBER OF SERVINGS FOR EACH ITEM LISTED

  ST= Starch (bread, pasta, cereal, rice, etc.)
  MT= Meat (poultry, beef, fish, eggs, nuts)
  V=Vegetable
  FR= Fruit
  D= Dairy (milk, yogurt, cheese, etc.)
  FT= Fat (butter, oil)
  B= Beverage (regular soft drinks, sweet tea, sports drinks, etc.)

Please be as specific and thorough as possible with the dietary information you provide. Thank You!

Time	Food	Quantity	Exchange

Appendix 8

EForm Name: IRB EPORTFOLIO
Page: 31. ATTACHMENTS
Section:
Question: Clean Copy
File Name: flyer.220525.pdf

Cystic Fibrosis Research Study

We are seeking volunteers to participate in a study to test whether a ketone ester supplement can reduce inflammation in the lungs for patients with cystic fibrosis.

Inclusion criteria:

- Diagnosed with cystic fibrosis
- >19 years old

Exclusion criteria:

- Concurrent or recent use of corticosteroids
- Acute respiratory failure requiring invasive or noninvasive ventilation
- Chronic liver or renal disease
- Pregnancy

Potential benefits:

- Reduction of inflammation in the lungs and blood
- Improved health outcomes

Compensation:

Participants will receive $300.00 upon full completion of this 7-day study.

If you are interested in participating in this study, please contact:

Jonathan Bergeron
Email: jbergeron@uabmc.edu
Phone: (205)-638-2220

Appendix 9

EForm Name: IRB EPORTFOLIO
Page: 31. ATTACHMENTS
Section:
Question: Clean Copy
File Name: KETONE CF DSMP_17June2022.docx

Data safety monitoring plan for: ***Ketone monoester supplementation in cystic fibrosis: A pilot and feasibility study***

Principal Investigator: ***Eric P. Plaisance, Ph.D.***
Grant Application: Pilot and Feasibility

Introduction

This randomized controlled trial (RCT) aims to evaluate the effectiveness of a commercially available ketone supplement on pulmonary function and markers of inflammation and metabolic health in patients with cystic fibrosis (CF) admitted for acute pulmonary exacerbation and a cohort of stable outpatient CF subjects. To accomplish this goal, a 5-7 day RCT will be conducted to compare the effects of ketone supplementation to a placebo control. The primary outcome will be differences in pulmonary function, namely $FEV_{1.0}$, FVC, and $FEV_{1.0}$/FVC. Secondary outcomes will include quantitative assessment of circulating insulin, glucose, and a number of inflammatory markers associated with the NLRP3 inflammasome. Qualitative assessment of tolerability and the feasibility of delivery will also be extensively examined. Compared to placebo control and standard care, we hypothesize that the ketone ester (KE4, KetoneAid, Falls Church, VA) will produce greater reductions in markers of inflammation and improvements in pulmonary function. We further hypothesize that ketone supplementation will be well-tolerated and prove to be feasible as it relates to administration and consumption of the ketone. Of note, this Ketone supplement is considered GRAS and does not require FDA IND or FDA oversight.

The intervention and measurement protocols pose minimal risk to participants (as described below). Because of this low-risk status, the data safety monitoring plan (DSMP) for this trial focuses on close oversight by Medical Monitor, Dr. Bryan Garcia. We will also provide prompt reporting of excessive adverse events and any serious adverse events to the Cystic Fibrosis Center, IRB at the University of Alabama at Birmingham (UAB) and NIH. The data safety monitoring plan (DSMP) outlined below will adhere to the protocol approved by the UAB IRB.

Safety reports will be sent to the study statistician, the MPIs, and to medical oversight at the schedule specified below in the table. The project coordinator will be responsible for assembling the data and producing these reports, as well as assuring that all parties obtain copies of these reports. The frequency of data review for this study differs according to the type of data and can be summarized in the following table:

Data type	**Frequency of review**
Subject accrual (adherence to protocol regarding demographics, inclusion/exclusion)	After every 5 patients that complete the study
Adverse event rates (e.g. gastrointestinal distress or dizziness)	As they occur (cumulative reports also reviewed quarterly)
Serious Adverse Events	Immediate reporting (within 24 hrs) to IRB
Compliance to treatment	After every 5 patients that complete the study

Qualifications and responsibilities of Medical/Safety Oversight
Dr. Bryan Garcia will serve as medical monitor for this study. Dr. Garcia is an Assistant Professor of Medicine at UAB. He has conducted numerous CF-related clinical trials and has extensive experience serving as a Co-Investigator for NIH-funded studies. As Medical Monitor, Dr. Garcia will review the reports sent by the project coordinator (at the frequency outlined above) to determine whether there is any corrective action, trigger of an *ad hoc* review, or stopping rule violation that should be communicated to the study investigator, UAB IRB, and NIH.

Measurement and reporting of participant accrual, adherence to inclusion/exclusion criteria and site performance Review of the rate of participant accrual and adherence to pre-specified inclusion/exclusion criteria will occur after the recruitment of every five patients throughout the study. During this phase, the target is to enroll approximately five patients per quarter. No specific subgroups will be tracked. We envision a high retention rate as this study will be conducted in an inpatient setting and will have close follow-up in the outpatient cohort. The quarterly review will assess this enrollment rate as well as to assure that participants meet eligibility criteria as outlined in the grant proposal. To accomplish this, the study statistician will oversee the preparation of data tables summarizing recruitment and enrollment status and demographic characteristics. In the event that participant accrual rates fall below projected levels, the study investigators will convene a conference call to discuss potential strategies to modify the recruitment, screening, and/or enrollment protocols for future recruitment efforts and will report any requested changes to the UAB IRB, medical/safety officer, and NIH.

Data integrity: All data will be collected by the study coordinator, Jonathan Bergeron, and inputted into Excel ~~Redcap~~ on secure UAB network. This data can be converted to other statistical analysis software. Relational logic checks, such as out-of-range values and internal inconsistencies, will be developed and automatically run in parallel with data entry. Double-data entry of study outcomes will be used to further minimize and detect entry errors. Statistical reports will be generated and include: 1) total number of participants screened, consented, and randomized on study entry and follow-up, and 2) a summary of demographic and baseline characteristics. This data will be password protected and only accessible by the PI and study coordinator.

Confidentiality: Every effort will be made to maintain the confidentiality of participant data by the investigator and the Institutional Review Board (IRB) to the extent permitted by law. All participants will be assigned subject ID numbers so personal health information (PHI) will not be used to identify participants.

Measurement and reporting of adverse events
We plan to collect adverse event data from all participants in both treatment conditions on a daily basis throughout the study. Potential symptoms include nausea, vomiting, lightheadedness, and abdominal pain. Participants who report clinically relevant adverse events will be immediately referred to the PI (Dr. Plaisance) and the Medical Monitor (Dr. Garcia) for additional evaluation and referral as appropriate. After

randomization, should the PI and research team determine that continued participation is contraindicated, the participant may be withdrawn from the study. Given that this is minimally invasive study, we do not anticipate that withdrawals will be common.

Other risks for this study are also judged minimal. Exogenous ketones have been shown to stimulate insulin secretion leading to mild reductions in blood glucose. We do not anticipate more than a 5-7% decrease in circulating glucose and do not anticipate symptomatic hypoglycemia. In the event that a patient presents with symptomatic hypoglycemia, our Study Coordinator, Jonathan Bergeron, will contact Dr. Garcia immediately.

Measurement and reporting of participant compliance to treatment protocol

Once randomized participants begin the intervention, data on treatment adherence will be monitored by research staff on an ongoing basis. Adherence will be measured as the number of times the participant consumes the placebo or ketone supplement. Adherence will be reviewed after every 5 participants or quarterly (whichever comes first) and if the safety officer has concerns about whether compliance has reached a level that might inhibit the ability of the study to test its primary hypotheses, he will suggest a conference call for study investigators to discuss methods for improving compliance.

Statistical analyses and stopping rules

Although no formal power analysis was conducted for this study (due to exploratory nature of the study as pilot and feasibility), our 2:1 (ketone:placebo) recruitment strategy will provide opportunity to detect smaller differences in the ketone treated group. We plan for no interim efficacy analyses and will not unblind until recruitment is complete. In this minimal-risk study, it is more likely that drop-outs or difficulty in recruiting adequate numbers of participants will require stopping the trial than that excess adverse events will occur and require stopping the trial. However, as outlined elsewhere, we will monitor adverse event rates in all participants and aggregate by randomized group. The safety officer, together with the PI, will alert the UAB IRB and the NIH if a larger than reasonably expected adverse event rate should occur in either treatment condition. Other issues relating to stopping rules for this trial include:

<u>New Information</u>

It is exceedingly unlikely that any new information will become available during this trial that would necessitate stopping the trial.

<u>Limits of Assumptions</u>

It is possible that baseline differences between the groups, excessive study dropouts, and/or missing data by the interim measurement time points will limit the value of data analysis of measurements. Baseline differences will be evaluated and effects on the power to detect differences in the primary outcome will be evaluated and communicated to the PIs, and safety office. Given the monitoring plans outlined elsewhere in this document as well as the randomized design of this study, it is exceedingly unlikely that there will be baseline differences between groups of any magnitude to threaten the validity of the study.

Limits of Rules

We acknowledge that there are other situations that could occur that might warrant stopping the trial and have a section in the safety report/checklist to identify other situations that might be of safety concern, which will allow for communication of concerns to the study MPIs, statistician, and safety officer.

Informed consent

After prospective participants have been preliminarily screened for eligibility and informed about the details of the study protocol, they will be asked to review the informed consent document. They will have the opportunity to ask questions and discuss all aspects of the study prior to providing consent. Informed consent will be obtained by the study coordinator or other designated research personnel with IRB clearance and appropriate training in the conduct of human research. It will be made clear that participation is voluntary and refusal to participate will not affect their eligibility or standing in other studies or programs at UAB nor will it affect the clinical care or other services they receive from their primary care physician.