PROTOCOL TITLE:

A Novel Nutrition Supplement for People with Cystic Fibrosis

PRINCIPAL INVESTIGATOR:

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VERSION NUMBER/DATE:

Version: 2

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Revision History

Version Date	Summary of Changes	Consent Change?
25Apr2025	Updating liver labs, correcting manufacturer	Yes

1.0 Study Summary

Study Title	A Novel Nutrition Supplement for People with Cystic Fibrosis
Study Design	Blinded, Single Center, Prospective, Intervention
Primary Objective	Determine if a novel form of vitamin D works better than the usual form in people with cystic fibrosis
Secondary Objective(s)	Determine if novel forms of vitamin E, Coenzyme Q10 (CoQ), and copper work better than the usual forms in people with cystic fibrosis
Research Intervention(s)/ Investigational Agent(s)	A mixture of micellular preparations of fat-soluble vitamin D, vitamin E, coenzyme Q_{10}, choline, Longvida® curcumin and copper
IND/IDE #	N/A
Study Population	Males and females, 18 years and older with a diagnosis of cystic fibrosis and exocrine pancreatic insufficiency
Sample Size (finite #, no estimates) (Other sites + Local = TOTAL)	60 (30 active and 30 control); 30 people receiving the novel forms of vitamins and 30 people receiving generic forms
Study End Date	December 31st, 2028
Study Specific Abbreviations/ Definitions	CF = cystic fibrosis CFQ-R = Cystic Fibrosis Questionnaire-Revised CoQ_{10} = coenzyme Q_{10}

2.0 Objectives

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

Aim 1 (primary objective): Determine how a novel versions of vitamin D affect the plasma levels of this nutrient compared to a traditional forms of vitamins D.

Aim 2 (secondary objective): Determine how select versions of vitamin E and CoQ affect plasma measures of these nutrients and affect plasma oxidized LDL (an indicator of vitamin E function), compared to generic versions of vitamin E and CoQ.

Aim 3 (secondary objective): Determine how copper glycinate + curcumin affect blood indicators of copper function compared to copper function alone.

We hypothesize that a 6-week supplementation with novel forms of fat-soluble nutrients (vitamins D and E, and CoQ_{10}), and copper with added curcumin, will increase blood levels of these fat-soluble vitamins, as well as improve blood measures of copper function. It is further hypothesized that these improvements will exceed those produced by conventional vitamins D and E and CoQ_{10}, as well as by copper.

3.0 Background

- Describe the relevant prior experience and gaps in current knowledge.
- Describe any relevant preliminary data.
- Provide the scientific or scholarly background for, rationale for, and significance of the research based on the existing literature and how will it add to existing knowledge.

CF is known to cause nutritional problems. These problems are not corrected by giving high doses of the problem nutrients for CF patients. A few attempts have been made to give special forms of vitamin D, vitamin E, and copper but this has not worked as well as hoped. Therefore, it is appropriate to look at all the problem nutrients in forms that have a higher chance at normalizing blood levels for the fat-soluble vitamins, as well as normalizing blood readings for copper function.

Preliminary data: N/A for CF specific studies.

Progress has been made in treating CF, but treatment of secondary complications can still improve life spans and quality of life. One complication involves impaired absorption of fat-soluble vitamins as well as impaired body use of copper (1-5). Fat-soluble vitamins absorb with dietary fat, but fat malabsorption occurs in CF. There also seems to be an additional impairment mechanism for fat-soluble vitamin absorption in CF (6).

Several approaches have been tried to improve the absorption of fat-soluble vitamins in people with CF. These have included high doses of conventional forms of the vitamins, water miscible versions of the vitamin compounds, and vitamins bound to agents that make them more water dispersible. None of these approaches has been fully successful. For example, studies of conventional vitamins have not consistently normalized plasma levels (7). In another approach, AquADEKs, a former leading seller for CF nutritional products, uses water miscible versions of the fat-soluble vitamins. However, in research studies, this product has failed to normalize blood readings for these vitamins (8,9).

Another product called LYM-X-SORB™ was geared to improving fat-soluble vitamin status in people with CF but did not fare well in research (10). In this case, vitamins D and E status was not improved, changes for A and K related measures were small, and the latter resembled the changes achieved with a placebo. Other studies on various fat-soluble vitamin preparations in CF have also yielded less than ideal results (i.e., 11,12). Currently, a product series called MVW, which has no direct published research, is being marketed for CF. The fat-soluble vitamins in MVW are not present in novel forms.

A new approach is now being proposed that uses micellular preparations of fat-soluble vitamins. Although this approach has not been tested in people with CF, micellular vitamins D and E have done well in rats with fat malabsorption (13). Therefore, the micellular approach for fat-soluble nutrients merits consideration in CF.

People with CF are thought to often have problems with 3 minerals: zinc, copper, and magnesium. Copper and zinc deficiency has been found in some studies of people with cystic fibrosis (15-18). For copper, the glycinate form has worked well in a number of studies on people that don't have CF (i.e., 19,20). This form appears to be superior to copper oxide, the form used in many multi-vitamin-mineral supplements. Copper oxide is not considered effective in healthy people (14). Another supplemental form is copper gluconate. In three studies, this copper form did not show signs of efficacy (21-22). Alternatively, copper sulfate can be utilized, but it can produce stomach upset. So, copper glycinate would seem the copper

form of choice. However, in a study that involved Dr. Robert DiSilvestro and Dr. Karen McCoy (15), copper glycinate did not correct copper deficiency in people with CF (based on blood copper enzyme activities).

MVW does not add copper to its primary product. MVW does have a secondary product that can be added to their main formula. This secondary product contains copper glycinate that did not work well with CF patients. To combat this, curcumin, a non-essential nutrient from the spice turmeric, will be given since it may aid copper incorporation into its target enzymes (23).

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2. Li L, Somerset S. Digestive system dysfunction in cystic fibrosis: challenges for nutrition therapy. Dig Liver Dis 46:865-874 .
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4. Dougherty K, Schall J, Stallings V. Suboptimal vitamin K status despite supplementation in children and young adults with cystic fibrosis. Am J Clin Nutr 2010;92:660-667.
5. Rovner A, Stallings V, Schall J, Leonard M, Zemel B. Vitamin D insufficiency in children, adolescents, and young adults with cystic fibrosis despite routine oral supplementation. Am J Clin Nutr 2007;86:1694-1699.
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15. Best K, DiSilvestro RA, McCoy K, Gemma S. Copper enzyme activities in cystic fibrosis before and after copper supplementation plus or minus zinc. Metabolism 2004;53:37-41.
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23. Cao J, Wang T, Wang M. Investigation of the anti-cataractogenic mechanisms of curcumin through in vivo and in vitro studies. BMC Ophthalmol 2018;18:48.

4.0 Study Endpoints

- Describe the primary and secondary study endpoints.
- Describe any primary or secondary safety endpoints.

The project will look at indicators of functional status of the nutrients.

Primary endpoints are:

- Plasma concentrations of the fat-soluble nutrients: Plasma 25-OH-vitamin D will be done with an ELISA kit. Plasma vitamin E will be analyzed by high performance liquid chromatography (HPLC).
- CoQ_{10}: Plasma concentrations of this molecule will be measured. For a chemistry function test, plasma vitamin C-like reducing power will be assessed.
- Copper status assessors: Plasma copper concentrations will be done. The utility of this measure for status assessment carries limitations, but it represents the standard approach. However, other assessments will also be done. Dr. DiSilvestro has been at the forefront of developing and testing methods for examining small changes in copper status. Copper status will also be evaluated by plasma diamine oxidase activity. Dr. DiSilvestro has found that these activities show extreme sensitivity to small changes in

copper status. The same trend was found by an Irish laboratory. In addition, erythrocyte superoxide dismutase activities will also be measured because they show more day-to day reading stability than plasma diamine oxidase activities. In addition, curcumin can help with this aspect of copper function by increasing production of superoxide dismutase.

- Choline: Plasma choline will be measured.
- Subjective self-assessment: Cystic Fibrosis Questionnaire-Revised (CFQ-R) will be done, which is validated for health-related quality of life measures in CF.

Secondary endpoints are:

- Plasma glucose: Measurements may relate to vitamin D status. Curcumin may affect blood glucose in a way that works with vitamin D actions.
- Oxidized LDL: A measure of oxidant stress that can be reduced by vitamin E supplementation. Readings can also sometimes be reduced by increased intake copper. Curcumin could help vitamin E with its actions on oxidized LDL.

Primary safety endpoint: Increased readings for plasma alanine amino transferase (ALT) can serve as a measure of liver injury. Many of the nutrients under consideration here can actually lower these readings under some circumstances.

5.0 Study Interventions/ Investigational Agent

- Describe the study intervention and/or investigational agent (e.g., drug, device) that is being evaluated.

The doses and forms are based on various considerations. All products will be taken once a day at the same time as a meal. The new formulation will contain the fat-soluble vitamins D and E and CoQ_{10} as micelles produced with naturally occurring molecules. Copper will be given as a mineral glycinate. Longvida® Curcumin will be added to help copper uptake.

For the new formulation, the daily doses for the nutrients under study will be as follows:

Supplement	Capsule/Tablet #	Dose	Manufacturer
Nanoemulsin Vitamin D + Vitamin E + Coenzyme Q10, copper glycinate, Longvida curcumin	6 capsules	1500 IU Vitamin D3 200 IU Vitamin E 100 mg Coenzyme Q_{10} 2.5 mg Copper Bisglycinate Chelate 80 mg Curcumin	3Is and Elevate Health Sciences
Alpha-GPC (Alpha-Glyceryl Phosphoryl Choline)	2 capsules	600 mg (240 mg Choline)	Vesta Pharmaceuticals, Inc

The vitamin D dose is that recommended for CF supplementation by the Cystic Fibrosis Foundation (PDF attached to IRB submission). For the control formula, vitamins D & E will

be in a conventional molecular version. For vitamin D, the new formula dose equals that used in a supplement called MVW, which is used by many people with CF. The MVW dose falls within the range recommended by CFF. The vitamin E dose is in the upper end of the CFF recommendation range and equals the MVW dose (40,41).

The CFF does not make a recommendation for the rest of the nutrients of the present study. The new formulation copper dose of 2.5 mg is high compared to the current RDA of 0.9 mg, but the previous recommendation was 2 mg. Evidence exists that the ideal copper intake lies closer to the older recommendations (42) and CF may raise requirements.

For the comparison formula, the nutrient amounts will equal those of the test formula. The formulas are as follows:

Supplement	**Capsule/Tablet #**	**Dose**	**Manufacturer**
Conventional Vitamin D + Vitamin E + Coenzyme Q10, copper glycinate	6 capsules	1500 IU Vitamin D3 200 IU Vitamin E 100 mg Coenzyme Q_{10} 2.5 mg Copper Bisglycinate Chelate	3Is and Elevate Health Sciences
Choline Tartrate	2 capsules	250 mg Choline	IVC

In order for the study team and lab to remain blinded, subjects will be randomized through the usage of Investigational Drug Services (IDS). IDS will dispense the supplements directly to a research nurse. The research nurse will sign the chain of custody. IDS will package the vitamin capsules into bottles of 90 capsules each and dispense 3 bottles to every patient on Day 1 (6-week supply/42 days + 3-day buffer = 45-day supply. At 6 capsules/day this is 270 capsules). IDS split the tablet of Choline Tartrate into two tablets in order for all study participants to be taking the same number of vitamins per day. IDS will dispense 1 bottle of 90 choline tablets/capsules on Day 1 (6-week supply/42 days + 3-day buffer = 45-day supply. At 2 capsules/day this is 90 capsules). All supplements will be dispensed in standard amber prescription bottles in order to maintain the blind. The nurse will then give supplements to the patient. The patients will not know which version of the supplement they will receive. The results of the lab results (i.e. vitamin levels) will not be released to the patients as the samples will be de-identified.

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41. Armah SM. Fractional zinc absorption for men, women, and adolescents is overestimated in the current dietary reference intakes. J Nutr 2016;146:1276-1280.
42. Lukaski HC, Johnson PE. Dietary copper (Cu) at the recommended intake decreases muscle cytochrome c oxidase (CCO) activity and alters metabolic responses during exercise in men. FASEB J 2005:19:A982.

- Drug Device Handling: If the research involves drugs or device, describe your plans to store, handle, and administer those drugs or devices so that they will be used only on subjects and be used only by authorized investigators.

- *If the control of the drugs or devices used in this protocol will be accomplished by following an established, approved organizational SOP (e.g., Research Pharmacy SOP for the Control of Investigational Drugs, etc.), please reference that SOP in this section.*

Investigational Drug Services will follow their Drug, Storage, and Handling Policies.

- If the drug is investigational (has an IND) or the device has an IDE or a claim of abbreviated IDE (non-significant risk device), include the following information:
  - Identify the holder of the IND/IDE/Abbreviated IDE.
  - Explain procedures followed to comply with sponsor requirements for FDA regulated research for the following:

	Applicable to:		
FDA Regulation	***IND Studies***	***IDE studies***	***Abbreviated IDE studies***
21 CFR 11	***X***	***X***	
21 CFR 54	***X***	***X***	
21 CFR 210	***X***		
21 CFR 211	***X***		
21 CFR 312	***X***		
21 CFR 812		***X***	***X***
21 CFR 820		***X***	

N/A

6.0 Procedures Involved

- Describe and explain the study design.

At screening visit, informed consent will be obtained per NCH standards. A member of the study staff will explain the study to the subject. Informed consent will be documented on a written consent form. Depending on current vitamin regimen, consent will be obtained at screening visit or visit 1.

After enrollment in the study, subjects will be asked to discontinue their current vitamin regimen for three days. For 6 weeks, people 18 years and older, with CF and exocrine pancreatic insufficiency, will be given either the new formulation (with specialized nutrient forms) or the comparison formula (with generic nutrient forms). A blood sample of X mL will be taken before and after the 6 weeks. Liver safety labs (Hepatic Function Panel (Albumin, Total Bilirubin, Direct Bilirubin, Alkaline phosphatase, ALT, AST, Total Protein) and GGTP will be included at baseline, 2-weeks, and 6-weeks. No FDA approvals are required for this study. We plan to enroll 30 patients per group (60 total). The first group will receive the control supplement while the second will receive the novel formulation. Equal numbers of males and females will be included.

During visit 1, ~10 mL of blood will be drawn, and subjects will be given the vitamin diary along with vitamin instructions for the next 6 weeks. Subjects will also complete the Cystic Fibrosis Questionnaire-Revised (CFQ-R). A research nurse will distribute the supplements to patients during the visit.

Subjects will be instructed to take 6 Vitamin D + Vitamin E + CoQ10 + Copper + Curcumin capsules, and 2 choline capsules with one meal. If they are given the comparison formulas, subjects will be instructed to take 6 Vitamin D + Vitamin E + CoQ10 + Copper capsules, and 2 choline tablets with one meal.

During visit 2, ~6 mL of safety liver labs will be drawn to ensure no liver injury has occurred.

During visit 3, patients will return their vitamin diary and any remaining supplements. Another ~10 mL of blood will be drawn. Subjects will complete the Cystic Fibrosis Questionnaire-Revised (CFQ-R) again at this visit.

Blood collections: 2.5-3 mL of blood will be collected from participant prior to initiation of vitamin supplementation and after the 6-week course. The safety liver labs will involve ~6 mL being drawn. The 2.5-3 mL will be drawn directly into green-top heparin tubes. The plasma should be separated and stored in 4 small tubes of any kind and frozen at -75 degrees Centigrade. For the remaining samples, the buffy coat should be removed with the top section of red blood cells. For the remaining red blood cells, about 1 mL cold phosphate buffered saline (Sigma Chemical Co or other source) is added gently in the blood draw tubes. Shaking is not needed. This can be stored in the refrigerator for up to 5 days until Dr. DiSilvestro or someone else assigned by the principal investigator picks them up.

Vitamins will be distributed to the patients through Investigational Drug Services at NCH.

- Provide a description of all research procedures being performed and when they are performed, including procedures being performed to monitor subjects for safety or minimize risks.

The following procedures will be done. Risks are stated along with the procedures.

- Blood draws: Risk of bruising, fainting, and minor risk of infection; done at Nationwide Children's Hospital.
- Capsule intake: Done at the site of the subject's choice (generally at home). Risk of choking. Risk not greater than that of everyday life. Risk of upset stomach. This is true of any nutrition supplement, but not more than usual for the types of supplement ingredients to be used here. Curcumin has some anecdotal reports of causing liver injury. In contrast, research studies have found that curcumin protects against liver injury. All of the other supplement nutrients are given in amounts that have no toxicity expectations. No major allergens should be present.

- Describe:
  - Procedures performed to lessen the probability or magnitude of risks.
  - All drugs and devices used in the research and the purpose of their use, and their regulatory approval status.
  - The source records that will be used to collect data about subjects. (Attach all surveys, scripts, and data collection forms.)

Blood draw risk reduction will be minimized by using professional phlebotomists or nurses in a clean setting. The blood volume collected will be limited to about 5-6 mL total. Sample

collection will take place in the outpatient lab in coordination with clinical labs or in CF clinic. Patients will be asked to return in 6 weeks after first visit for a research-only visit.

Curcumin risks to the liver will be minimized by excluding anyone with known liver problems. The relatively short study duration of 6 weeks minimizes chances of liver injury which would likely be slow developing if such injury does occur.

Risk of upset stomach is minimized by having subjects take the supplements in the middle of a meal.

- What data will be collected during the study and how that data will be obtained.

Data will consist of blood analysis done on samples collected before and after the 6-week intervention.

Pancreatic sufficiency, modulator usage, genotypes, age, and previous vitamin levels will be collected from the EMR.

- If there are plans for long-term follow-up (once all research related procedures are complete), what data will be collected during this period.

N/A

- For Humanitarian Use Device (HUD) uses provide a description of the device, a summary of how you propose to use the device, including a description of any screening procedures, the HUD procedure, and any patient follow-up visits, tests or procedures.

N/A

7.0 Study Timelines

- Describe:
  - The duration of an individual subject's participation in the study.
  - The duration anticipated to enroll all study subjects.
  - The date for the investigators to complete this study (complete primary analyses, study closure in eIRB2).

Subjects will be enrolled in this study for 6 weeks. Subjects will be enrolled gradually over 3 months. The study will be completed in 12 months.

8.0 Inclusion and Exclusion Criteria

- Describe how individuals will be screened for eligibility.
- Describe the criteria that define who will be included or excluded in your final study sample.
  - Please include the age range that will be used ("birth to adult" or specify age range (e.g. 2 years old to 10 years old)

A list of patients 18 years of age and older with pancreatic insufficiency will be pulled from the EMR/CF Registry. From that list, study staff will screen and approach eligible patients to see if they would like to participate.

Inclusion:

- Diagnosed with cystic fibrosis
- Diagnosed with exocrine pancreatic insufficiency
- 18 years old or older
- Currently on modulator
- Willing to participate
- Normal liver enzyme labs

Exclusion:

- Non-English-speaking participants
- Acute health crisis
- Persistent elevation of liver enzymes >6 months (E2) (ALT >80 U/L)
- History of liver abnormalities
- If patients are currently taking Category A or Category B in the LiverTox categorization system (https://www.ncbi.nlm.nih.gov/books/NBK548392/) study staff will ask a CF pharmacist for review of patient chart and approval to enroll.
- Recent vitamin D supplementation of 30 mcg/day or higher, vitamin E supplements of 200 IU/day or higher, or copper at 2 mg/day or higher
- Any other concern by investigator that the subject is inappropriate for inclusion
- Patients who is on a reduced dose of a CFTR modulator
- Patients on azole antifungals (voriconazole, itraconazole, posaconzole, >7 days of fluconazole, etc.).
- Patients who binge drink EtOH – for men more than 2 drinks/day, for women more than 1 drink/day
- Patients that are on other medications that are sensitive CYP3A4 substrates – such as tacrolimus for example
- Patients on sensitive CYP3A4 substrates including but not limited to tacrolimus, sirolimus, and cyclosporine

- Indicate specifically whether you will include or exclude each of the following special populations: (You may not include members of the above populations as subjects in your research unless you indicate this in your inclusion criteria.)
  - Adults unable to consent
  - Individuals who are not yet adults (infants, children, teenagers)
  - Pregnant women
  - Prisoners

We will not be including any of these special populations.

9.0 Vulnerable Populations

If the research involves individuals who are vulnerable to coercion or undue influence:

- Check the box for the vulnerable population(s) involved.
- Review the appropriate checklist (do *not* include in submission).
- Describe additional safeguards included to protect their rights and welfare.

☐ Research involving pregnant women, reference "CHECKLIST: Pregnant Women (HRP-412)"

N/A

☐ The research involves neonates of uncertain viability or non-viable neonates, review "CHECKLIST: Neonates (HRP-413)" or "HRP-414 – CHECKLIST: Neonates of Uncertain Viability (HRP-414)" to ensure that you have provided sufficient information.

N/A

☐ The research involves prisoners, review "CHECKLIST: Prisoners (HRP-415)" to ensure that you have provided sufficient information.

N/A

☐ The research involves persons who have not attained the legal age for consent to treatments or procedures involved in the research ("children"), review the "CHECKLIST: Children (HRP-416)" to ensure that you have provided sufficient information.

N/A

☐ The research involves cognitively impaired adults, review "CHECKLIST: Cognitively Impaired Adults (HRP-417)" to ensure that you have provided sufficient information.

N/A

10.0 Local Number of Subjects

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

We plan to enroll 60 CF patients; 30 subjects receiving the novel forms of nutrients and 30 subjects receiving generic forms.

11.0 Withdraw of Subjects

- Describe anticipated circumstances under which subjects will be withdrawn from the research without their consent.
- Describe any procedures for orderly termination.
- Describe procedures that will be followed when subjects withdraw from the research, including partial withdrawal from procedures with continued data collection.

Subjects may withdraw study consent at any time via written or oral notification to one of the study team members. No further study collections will take place.

12.0 Risks to Subjects

- List the reasonably foreseeable risks, discomforts, hazards, or inconveniences to the subjects related the subjects' participation in the research. Include as may be useful for the IRB's consideration, a description of the probability, magnitude, duration, and reversibility of the risks. Consider physical, psychological, social, legal, and economic risks.

We believe there is very little chance of harm with this study.

Drawing blood by placing a needle in a vein may cause pain, lightheadedness, fainting, bleeding, bruising, or swelling at the puncture site. Infection is a rare possibility.

Consuming the supplement may present a risk of choking. The supplement may also cause an upset stomach; this is true of any nutrition supplement.

Curcumin has some anecdotal reports of causing liver injury. In contrast, research studies have found that curcumin protects against liver injury. All of the supplement nutrients are given in amounts that have no toxicity expectations. No major allergens are present.

There is a possible risk of incidental findings. A severe nutritional deficiency or signs of liver injury could be found. In that case, the subjects will be referred to their primary care physician.

- Describe what actions will be taken to minimize the risks (listed above).

Blood draw risk reduction will be minimized by using professional phlebotomists in a clean setting. The blood volume collected will be limited to about 10 mL. Curcumin risks to the liver will be minimized by excluding anyone with known liver problems. The relatively short study duration of 6 weeks minimizes chances of liver injury which would likely be slow developing if such injury does occur. Risk of upset stomach is minimized by having subjects take the supplements in the middle of a meal.

Safety liver labs will be drawn at baseline, 2-weeks, and 6-weeks to ensure no injury to liver.

- If applicable, indicate which procedures may have risks to the subjects that are currently unforeseeable. (Include what actions will be taken to minimize the risks.)

N/A

- If applicable, indicate which procedures may have risks to an embryo or fetus should the subject be or become pregnant. (Include what actions will be taken to minimize the risks.)

N/A

- If applicable, describe risks to others who are not subjects. (Include what actions will be taken to minimize the risks.)

N/A

13.0 Potential Benefits to Subjects

- Describe the potential benefits that individual subjects may experience from taking part in the research. (Consider and include the probability, magnitude, and duration of the potential benefits).

  OR

- Indicate if there is no direct benefit. Do not include benefits to society or others.

The supplements could potentially improve the patient's vitamin and nutritional status and associated physiological functions.

14.0 Data Management and Confidentiality

- Describe the data analysis plan, including any statistical procedures or power analysis.

For this project, like most projects, a p value of 0.05 or less will be accepted as statistically significant. For the blood tests, in each treatment group, the initial and final readings will be compared to each other by a paired t-test. This analysis tells whether either treatment produced a statistically significant change. After this analysis, for each type of blood measure, the data will be recalculated for each subject as the change in readings (final minus initial). This data will be used to test the main hypothesis: for each type of measure, the novel nutrient forms will give bigger changes than the conventional form for measures related to the primary and secondary endpoints without a difference in the safety endpoint. For each type of measure, the change in values for the novel nutrient group will be compared to conventional group change. This comparison will be done by unpaired t test. Although a $p < 0.05$ will be accepted for showing statistical significance, a distinction strong and consistent enough to produce a $p < 0.01$ would be preferable (since the hope for the study is to produce compelling justification for future work).

A power calculation was done based on the 25-OH-vitamin D response to vitamin D supplementation. The power calculation takes into account that a major goal of the study is to see if one version of vitamin D works better than another. Therefore, the power calculation is based on the unpaired comparison for the change in values for one group versus the change in the other. A minimal difference was set 6 ng/mL for the novel vitamin D versus 2 ng/mL for conventional vitamin D with a variance of 2.8. For a power value of 0.80, $p = 0.01$, a sample size per group is 30.

- Describe the steps that will be taken to secure the data (e.g., training, authorization of access, password protection, encryption, physical controls, certificates of confidentiality, and separation of identifiers and data) during storage, use, and transmission.

To protect the confidentiality of the participants, names will be removed from each participant's file and replaced with an identification code. All testing protocols will use these codes to identify subjects. A list that contains the match between the code and name will be kept in a secure location only accessible to the investigators. All data will be retrieved using the identification code. Data will be maintained on a secure password protected computer database only accessible to the investigators.

Privacy will be protected by requiring that all study-related interactions with subjects be conducted in a private clinic room. Information about study subjects will be kept confidential and will be protected by restricting access to the data to investigators directly associated with the study and by storing identifiable paper copies of information in locked file cabinets. Indirectly identifiable data is stored separately from linkage information.

- Describe any procedures that will be used for quality control of collected data.

Data management and study coordination will be centrally coordinated using an online software program, REDCap, provided by NCH or excel database. This secure data management program will unify protocol adherence and maintain data integrity and compliance. Data management will occur locally using the online data entry and subject tracking capabilities at Nationwide Children's Hospital.

- Describe how data or specimens will be handled study-wide:

- What information will be included in that data or associated with the specimens?
- Where and how data or specimens will be stored?
- How long the data or specimens will be stored? (Must be kept for a minimum of 6 years, once deidentified may be kept longer if specified)
- Who will have access to the data or specimens?
- Who is responsible for receipt or transmission of the data or specimens?
- How data or specimens will be transported?

All specimens will be transported in secure bio-safety containers until storage in Dr. Tonya Orchid's Lab at the Ohio State University. All specimens will be labeled with a study ID# and remain de-identified. Specimens will be stored until processed/analyzed. Extra specimens will be stored for future research in a specimen bank, which is included in the consent. Data will be stored for 6 years after study completion in a password protected database. Data and specimens will be available to the study team investigators only. Specimens IDs will be linked to clinical data in a password-protected database available to the PIs.

15.0 Provisions to Monitor the Data to Ensure the Safety of Subjects

*****This section is required when research involves more than Minimal Risk to subjects.***

- Describe:
  - The plan to periodically evaluate the data collected regarding both harms and benefits to determine whether subjects remain safe. The plan might include establishing a data monitoring committee and a plan for reporting data monitoring committee findings to the IRB and the sponsor.
  - What data are reviewed, including safety data, untoward events, and efficacy data
  - How the safety information will be collected (e.g., with case report forms, at study visits, by telephone calls with participants).
  - The frequency of data collection, including when safety data collection starts.
  - Those responsible to review the data.
  - The frequency or periodicity of review of cumulative data.
  - The statistical tests for analyzing the safety data to determine whether harm is occurring.
  - Any conditions that trigger an immediate suspension of the research.

N/A

16.0 Provisions to Protect the Privacy Interests of Subjects

- Describe the steps that will be taken to protect subjects' privacy interests. "Privacy interest" refers to a person's desire to place limits on whom they interact or whom they provide personal information.
- Describe what steps you will take to make the subjects feel at ease with the research situation in terms of the questions being asked and the procedures being performed. "At ease" does not refer to physical discomfort, but the sense of intrusiveness a subject might experience in response to questions, examinations, and procedures.
- Indicate how the research team is permitted to access any sources of information about the subjects.

Subjects will be approached during clinic visits and asked if they would like to hear more information about the research study. Subjects can opt to hear this information in clinic setting or alone/with caregiver/over the phone.

Questions and concerns related to study information and vitamin supplementation will be reviewed with the subject and all questions will be answered.

Study staff are only allowed to access patient information as recorded. The use of EPIC medical charts is required for medical history.

Research staff will be primarily accessing de-identified data when compiling statistical analysis. Information will be entered in by as few research team members as possible to minimize subject information across individuals. The list linking the study ID to the subject will be kept separate from the research data. All study data will be stored on the NCH secure server with access only by the research team. PI or designated research team members will receive, transmit and store data per these parameters. All data stored and collected will be within NCH by approved research staff.

17.0 Data and Specimen Banking

Data and/or Tissue "banking" refers to data and/or tissue that will be stored in large databanks or tissue banks for future research. This does not refer to storage of data during a specific ongoing study that is not going to be shared with a large data bank. Data for one study is stored by the investigator in a secure manner can be described in the Data Management section in the protocol.

- If data or specimens will be banked for future use (*not* for use with this study only), describe where the data and/or specimens will be stored, how long they will be stored, how the data and/or specimens will be accessed, and who will have access to the data and/or specimens.
- List the data to be stored or associated with each specimen.
- Describe the procedures to release data or specimens, including: the process to request a release, approvals required for release, who can obtain data or specimens, and the data to be provided with specimens.

Specimens to be analyzed and/or data to be collected include 5-6 mL of blood. Each stored specimen will have a study ID and date. Key clinical data such as demographics, genotype, medications, nutritional status, presence of chronic pulmonary infections, presence of key co-morbid conditions, and other relevant data will also be collected and stored in a password-protected electronic database maintained by research staff.

18.0 Sharing of Results with Subjects

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

Individual results will not be shared with the participants. If interested, group results can be shared with the participants after study closure and analysis of data. In the case of an acutely dangerous nutritional deficiency condition, results will be shared with participants and their primary care physician.

19.0 Recruitment Methods

- Describe when, where, and how potential subjects will be recruited.
- Describe the source of subjects.
- Describe the study team member's relationship to the potential participant.
- Describe the methods that will be used to identify potential subjects.
- Describe materials that will be used to recruit subjects. (Attach copies of these documents with the application. For advertisements, attach the final copy of printed advertisements. When advertisements are taped for broadcast, attach the final audio/video tape. You may submit the wording of the advertisement prior

to taping to preclude re-taping because of inappropriate wording, provided the IRB reviews the final audio/video tape.)

Subjects with CF who are deemed eligible will be identified for this study and approached by research staff during routine clinical visits, hospitalizations, other modes of telehealth, or by phone.

Subjects will be enrolled from the CF Clinic at NCH.

A list of patients 18 years of age and older with pancreatic insufficiency will be pulled from the EMR/CF Registry. From that list, study staff will screen and approach eligible patients to see if they would like to participate.

There will be no advertisements.

20.0 Process to Document Consent in Writing

- Describe whether you will be following "SOP: Written Documentation of Consent (HRP-091)." If not, describe whether and how consent of the subject will be documented in writing.

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

***If you will document consent in writing, attach a consent document. If you will obtain consent, but not document consent in writing, attach a consent script. Review "CHECKLIST: Waiver of Written Documentation of Consent (HRP-411)" to ensure that you have provided sufficient information. You may use "TEMPLATE CONSENT DOCUMENT (HRP-502)"to create the consent document or script.*

Subjects will be asked to sign a study consent form after receiving a complete explanation of the study. We will follow SOP: Informed Consent Process for Research (HRP-090).

Consent will be obtained following NCH "SOP: Written Documentation of Consent (HRP-091)." Consent documents are attached to the IRB submission.

21.0 Consent Process

- Indicate whether you will be obtaining consent, and if so describe:
  - Where will the consent process take place.
  - Any waiting period available between informing the prospective subject and obtaining the consent
  - Any process to ensure ongoing consent.
  - Whether you will be following "SOP: Informed Consent Process for Research (HRP-090)." If not, describe:
    - The role of the individuals listed in the application as being involved in the consent process.
    - The time that will be devoted to the consent discussion.
    - Steps that will be taken to minimize the possibility of coercion or undue influence.
    - Steps that will be taken to ensure the subjects' understanding.

A member of the study staff will explain the study to the subject. Informed consent will be documented on a written consent form. Informed consent will take place in a quiet room in the clinic.

Consent may be collected via electronic consent by telephone. Under the guidance of the Investigator Manual in eIRB, page 16 concerning eConsent:
When patient is consenting via eConsent, study staff will send the electronic consent via Research Electronic Data Capture (REDCap). Study staff will read the consent with the subject and answer any questions. Subject will sign the electronic copy in real time. Once the signed consent is submitted, study staff will receive an email, sign the "person obtaining consent" portion, save and securely email a copy to the patient.

Considerations for Consent Process

☐ ***Waiver or Alteration Consent Process (consent will not be obtained, required information will not be disclosed, or the research involves deception)***

- Provide a justification for the waiver or alteration in the response box below.
- Review the "CHECKLIST: Waiver or Alteration of Consent Process (HRP-410)" to ensure you have provided sufficient information for the IRB to make these determinations.
- If the research involves a waiver the consent process for planned emergency research, please review the "CHECKLIST: Waiver of Consent for Emergency Research (HRP-419)" to ensure you have provided sufficient information for the IRB to make these determinations.

N/A

☐ ***Waiver of Written Documentation of Consent (verbal, virtual, and/or eConsent without signature)***

- Review the "CHECKLIST: Waiver of Written Documentation of Consent (HRP-411)" to ensure you have provided sufficient information for the IRB to make these determinations.

N/A

Non-English Speaking Subjects- (if not known, skip)

- Indicate what language(s) other than English are understood by prospective subjects or representatives.
- If subjects who do not speak English will be enrolled, describe the process to ensure that the oral and written information provided to those subjects will be in that language. Indicate the language that will be used by those obtaining consent.

Non-English-speaking subjects will not be enrolled at this time. If there are non-English speaking subjects that become eligible for the study, research staff will take all precautions to ensure consenting and participation are in accordance with federal guidelines.

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

- Describe the criteria that will be used to determine whether a prospective subject has not attained the legal age for consent to treatments or procedures involved in the research under the applicable law of the jurisdiction in which the

N/A

research will be conducted. (E.g., individuals under the age of 18 years.) o For research, conducted in the state, review "SOP: Legally Authorized Representatives, Children, and Guardians (HRP-013)" to be aware of which individuals in the state meet the definition of "children." o For research, conducted outside of the state, provide information that describes which persons have not attained the legal age for consent to treatments or procedures involved the research, under the applicable law of the jurisdiction in which research will be conducted. One method of obtaining this information is to have a legal counsel or authority review your protocol along the definition of "children" in "SOP: Legally Authorized Representatives, Children, and Guardians (HRP-013)." • Describe whether parental permission will be obtained from: o Both parents unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child. o One parent even if the other parent is alive, known, competent, reasonably available, and shares legal responsibility for the care and custody of the child. • Describe whether permission will be obtained from individuals other than parents, and if so, who will be allowed to provide permission. Describe the process used to determine these individuals' authority to consent to each child's general medical care. • Indicate whether assent will be obtained from all, some, or none of the children. If assent will be obtained from some children, indicate which children will be required to assent. • When assent of children is obtained describe whether and how it will be documented.	
Cognitively Impaired Adults • Describe the process to determine whether an individual is capable of consent. The IRB allows the person obtaining assent to document assent on the consent document and does not routinely	N/A

require assent documents and does not routinely require cognitively impaired adults to sign assent documents.	
Adults Unable to Consent • List the individuals from whom permission will be obtained in order of priority. (E.g., durable power of attorney for health care, court appointed guardian for health care decisions, spouse, and adult child.). o For research conducted in the state, review "SOP: Legally Authorized Representatives, Children, and Guardians (HRP-013)" to be aware of which individuals in the state meet the definition of "legally authorized representative." o For research conducted outside of the state, provide information that describes which individuals are authorized under applicable law to consent on behalf of a prospective subject to their participation in the procedure(s) involved in this research. One method of obtaining this information is to have a legal counsel or authority review your protocol along the definition of "legally authorized representative" in "SOP: Legally Authorized Representatives, Children, and Guardians (HRP-013)." • Describe the process for assent of the subjects. Indicate whether: o Assent will be required of all, some, or none of the subjects. If some, indicate which subjects will be required to assent and which will not. o If assent will not be obtained from some or all subjects, an explanation of why not. o Describe whether assent of the subjects will be documented and the process to document assent. The IRB allows the person obtaining assent to document assent on the consent document and does not routinely require assent documents and does not routinely require subjects to sign assent documents.	N/A
Consent for HUD • For HUD uses provide a description of how the patient will be informed of the potential risks	N/A

and benefits of the HUD and any procedures associated with its use.	

22.0 Compensation for Research-Related Injury

- If the research involves more than Minimal Risk to subjects, describe the available compensation in the event of research related injury.
- *Provide a copy of contract language, if any, relevant to compensation for research-related injury.*

N/A

23.0 Compensation to Subjects

- Describe the amount and timing of any payments to subjects.

Enrolled subjects will be compensated $30 after first blood draw, $30 after second blood draw, and $30 after third blood draw. If patients complete 90% of the 6 weeks (i.e., patients take the vitamins for 38 of the 42 days) patients will receive a $50 bonus. 90% supplement ingestion adherence will be measured by the number of supplements returned to study staff, along with their recordings in the vitamin diary.

Study Visit	Amount	Description
Visit 1	$30	Subjects will be paid $30 after first blood draw.
Visit 2	$30	Subjects will be paid $30 after second blood draw.
6-week adherence	$50	Subjects will receive a $50 bonus if they complete 90% of the 6 weeks. (38/42 days)
Visit 2	$30	Subjects will be paid $30 after third blood draw.

24.0 Economic Burden to Subjects

- Describe any costs that subjects may be responsible for because of participation in the research, e.g., fuel, parking, childcare.

As much as possible, at least one study visit will be coordinated with regularly scheduled clinic visits so that no extra transportation burden will be placed on the study subjects.

25.0 Setting

- Describe the local sites or locations where your research team will conduct the research.
  - Identify where your research team will identify and recruit potential subjects.
  - Identify where research procedures will be performed.
  - Describe the composition and involvement of any community advisory board.
  - For research conducted outside of the organization and its affiliates describe:
  - Site- specific regulations or customs affecting the research for research outside the organization.
  - Local scientific and ethical review structure outside the organization.

All research encounters will occur in the NCH CF clinic. Sample collection will take place in the outpatient lab in coordination with clinical labs or in CF clinic.

26.0 Resources Available

- Describe the resources available to conduct the research. For example, as appropriate:
  - Justify the feasibility of recruiting the required number of suitable subjects within the agreed recruitment period. For example, how many potential subjects do you have access to? What percentage of those potential subjects do you need to recruit?
  - Describe the time that you will devote to conducting and completing the research.
  - Describe your facilities.
  - Describe the availability of medical or psychological resources that subjects might need as a result of an anticipated consequences of the human research.
  - Describe your process to ensure that all persons assisting with the research are adequately informed about the protocol, the research procedures, and their duties and functions.

We hope to recruit 60 eligible subjects, 30 control and 30 active. We predict that we will be able to recruit the minimum number of eligible subjects within 12 months.

Study management, data collection and data analysis will include assistance from the Pulmonary Research Core at NCH. A research coordinator will be available for oversight of regulatory documents and to assist with consenting, subject recruitment, and enrollment.

The NCH CF Center has over 500 subjects and is a member of the CFF Therapeutics Development Network (TDN). This site participates in many clinical trials and investigator-initiated studies in which clinic space is utilized to conduct study visits. The NCH CF Center is well equipped to execute research studies.

All study staff will review the protocol and all relevant study documents and will be trained in the process of obtaining consent/assent, eligibility criteria, and carrying out study visits. All applicable study training will be documented via training log and saved electronically and/or in an investigator site file.

27.0 Confidentiality of Data Collection

- How long will identifying information on each participant be maintained? (Study data and identifiers must be stored for at least six years after study closure; a longer period may be used. A specific date or number of years must be listed.)

Identifying information of study subjects will be kept for six years after study closure then destroyed.

- Describe any plans to code identifiable information collected about each participant.

Study data will be stored in a REDCap or excel database. Subjects will be assigned a unique study ID that will be placed on the data form. The list linking the study ID to the subject will be kept separate from the research data. All study data will be stored on the NCH secure server with access only by the research team. PI or designated research team members will receive, transmit and store data per these parameters. All data stored and collected will be within NCH by approved research staff.

- Check each box that describes steps that will be taken to safeguard the confidentiality of information collected for this research:
  ☒ Research records will be stored in a locked cabinet in a secure location

☒ Research records will be stored in a password-protected computer file
☒ The list linking the assigned code number to the individual subject will be maintained separately from the other research data
☒ Only certified research personnel will be given access to identifiable subject information.

- Describe the provisions included in the protocol to protect the privacy interests of subjects, where "privacy interests" refer to the interest of individuals in being left alone, limiting access to them, and limiting access to their information. (This is not the same provision to maintain the confidentiality of data.)

Privacy interests will be discussed with the patient completing the study. PHI and clinical data collected will continue to be maintained securely as noted above.

- Will it be necessary to record information of a sensitive nature?
  "Sensitive information includes but is not limited to 'information relating to sexual attitudes, preferences, or practices; information relating to the use of alcohol, drugs, or other addictive products; information pertaining to illegal conduct; information that, if released, might be damaging to an individual's financial standing, employability, or reputation within the community or might lead to social stigmatization or discrimination; information pertaining to an individual's psychological well-being or mental health; and genetic information or tissue samples.'"

  ☐ Yes ☒ No

- Do you plan to obtain a federally-issued Certificate of Confidentiality as a means of protecting the confidentiality of the information collected? (If the study is NIH funded, Certificate of Confidentiality will be issued; please mark "Yes").
  "Certificate of Confidentiality (Certificate) protects the privacy of research participants enrolled in biomedical, behavioral, clinical, or other types of health-related research that collect or use identifiable, sensitive information. With limited exceptions, researchers may not disclose names or any information, documents or biospecimens containing identifiable, sensitive information. The Certificate prohibits disclosure in response to legal demands, such as a subpoena."

  ☐ Yes ☒ No

28.0 Protected Health Information (PHI) Recording

PHI: individually identifiable health information transmitted or maintained in any form (electronic means, on paper, or through oral communication) that relates to the past, present or future physical or mental health or conditions of an individual plus any of the following 18 identifiers.

Are you accessing or recording information related to the provision of healthcare or payment for healthcare services (medical records, lab test results, diagnoses, etc.)?
Consider sources such as the medical record, clinic schedules, billing statements, etc. This includes screening for potential subjects for recruitment purposes.

☒ If yes, complete section 28.0.
☐ If no, skip section 28.0.

Indicate which subject identifiers will be ACCESSED for this research.

☒ Name	☐ Account Numbers
☐ Address *(including street, city, state, zip code and county)*	☐ Certificate/License Numbers
	☐ Vehicle Identifiers and Serial Numbers

☒ Dates *(treatment dates, birth date, date of death)* ☒ Telephone ☐ Fax Number ☒ Email address, ☐ Social Security Number *(do not check if only used for ClinCard)* ☒ Medical Record Number or other account number (specify below) ☐ Health Plan Beneficiary Identification Number	☐ Device Identifiers and Serial Numbers ☐ URL ☐ IP address ☐ Biometric identifiers, including finger and voice prints ☐ Full face photographic images and/or any comparable images ☐ Other number, characteristic or code that could be used to identify an individual (specify below) ☐ None *(Complete De-identification Certification Form)*

If the "Medical Record Number or other account number) and/or "Other number, characteristic or code that could be used to identify an individual" please respond below.

Medical Record Number needed to verify patient eligibility.

Indicate which subject identifiers will be RECORDED for this research.

☒ Name ☐ Address *(including street, city, state, zip code and county)* ☒ Dates *(treatment dates, birth date, date of death)* ☒ Telephone ☐ Fax Number ☒ Email address, ☐ Social Security Number *(do not check if only used for ClinCard)* ☒ Medical Record Number or other account number (specify below) ☐ Health Plan Beneficiary Identification Number	☐ Account Numbers ☐ Certificate/License Numbers ☐ Vehicle Identifiers and Serial Numbers ☐ Device Identifiers and Serial Numbers ☐ URL ☐ IP address ☐ Biometric identifiers, including finger and voice prints ☐ Full face photographic images and/or any comparable images ☐ Other number, characteristic or code that could be used to identify an individual (specify below) ☐ None *(Complete De-identification Certification Form)*

If the "Medical Record Number or other account number) and/or "Other number, characteristic or code that could be used to identify an individual" please respond below.

Medical Record Number needed to access patients contact information for the follow up appointment.

29.0 Confidential Health Information Recording

Please mark all categories that reflect the nature of health information to be ACCESSED and USED as part of this research.

☒ Demographics *(age, gender, educational level)*	☐ Names of drugs and/or devices used as part of treatment
☒ Diagnosis	☐ Location of treatment
☒ Laboratory reports	☐ Name of treatment provider
☐ Radiology reports	☐ Surgical reports
☐ Discharge summaries	☐ Other information related to course of treatment
☐ Procedures/Treatments received	☐ None
☐ Billing information	

If the information you are collecting does not match any of the options listed above, please list what information you will be gathering.

N/A

30.0 Waiver or Alteration of HIPAA Research Authorization

- **Check the appropriate category and attach the required form on the Local Site Documents, #3. Other Documents, page of the application. (Mark all that apply.)**

  ☒ Protocol meets the criteria for waiver of authorization. (Continue filling out section 30.)
  ☒ Patient Authorization will be obtained. (Include the appropriate HIPAA language (see Section 14 of consent template) in the consent form OR attach the HRP-900, HIPAA AUTHORIZATION form.)
  ☐ Protocol is using de-identified information. (Attach the HRP-902, DE-IDENTIFICATION CERTIFICATION form.)
  ☐ Protocol involves research on decedents. (Attach the HRP-903, RESEARCH ON DECEDENTS REQUEST form.)
  ☐ Protocol is using a limited data set and data use agreement. (Contact the Office of Technology Commercialization to initiate a Limited Data Use Agreement.)

Find the HIPAA forms in the eIRB2 Website Library, Templates.

- Please indicate the type of waiver or alteration needed for this study.
  Note: If the research involves more than one type of waiver, check the appropriate box.

  ☒ A. Partial Waiver (to access PHI for recruitment purposes only)
  ☐ B. Full Waiver (entire research study)
  ☐ C. Alteration (waiver of written documentation of authorization; obtaining verbal authorization to use PHI)

- Please discuss why it is necessary to access and review the health information noted in your response above.

Patient pancreatic sufficiency status, age, and modulator usage are necessary to confirm the patient's eligibility for participation in the study.

- Is the health information to be accessed and reviewed the minimal necessary to achieve the goals of this research? Please provide an explanation, as well.

☒ Yes ☐ No
Study staff will only be accessing the necessary information to identify eligible patients to recruit.

- Explain how the access, use, or disclosure of PHI presents no more than a minimal risk to the privacy of the individual.

Study staff will only be accessing the necessary information to identify eligible patients to recruit.

- Describe your plan to protect the identifiers (or links to identifiable data) associated with the PHI from improper use and disclosure, including where PHI will be stored, what security measures will be applied, and who will have access to the information. Describe the safeguards for electronic and/or hard copy records.

Each enrolled patient will be given a unique identification number. Study data will be restricted to study staff only.

- Will identifiers (or links to identifiable data) be destroyed? Provide a justification for your answer.

☒ Yes – Describe the plan to destroy the identifiers at the earliest opportunity consistent with the conduct of the research. Include **when** (consistent with section 27) and **how** identifiers will be destroyed. ☐ No – Provide the legal, health, or research justification for retaining the identifiers. Legal justification should include a brief description/citation of the legal requirement. ☐ N/A – Will not record identifiers or create links or codes to connect the data.
Identifiers will be destroyed 6 years after study closure. IS will be contacted to aid in destruction.

- Explain why a waiver/alteration (instead of written authorization) is needed to conduct the research.

A partial waiver is required for recruitment purposes.

NOTE: Only those personnel listed on the IRB-approved application may access PHI and medical information.

Reminder: Protected Health Information obtained as part of this research will not be reused or disclosed to any other person or entity other than those listed (except as required by law for authorized oversight of the research project) without additional approval. IRB/Privacy Board approval must be obtained for other research involving the use or disclosure of this PHI.

31.0 Multi-Site Research

***This section is required when research will be conducted at multiple sites. Check the appropriate box.**

☐ NCH **IS** participating in multi-site research.
☒ NCH **IS NOT** participating in multi-site research. No further information is needed in this section.

- TOTAL Number of Subjects to be Enrolled Study-Wide
- List the locations of the additional sites. Please indicate which sites are International.

N/A

- Study-Wide Recruitment Methods

** If this is a multicenter study and subjects will be recruited by methods not under the control of the local site (e.g., call centers, national advertisements) describe those methods here. Local recruitment methods are described earlier in the protocol (Section 19.0).

- Describe when, where, and how potential subjects will be recruited.
- Describe the methods that will be used to identify potential subjects.
- Describe the materials that will be used to recruit subjects. (Attach copies of these documents with the application. For advertisements, attach the final copy of printed advertisements. When advertisements are taped for broadcast, attach the final audio/video tape. You may submit the wording of the advertisement prior to taping to preclude re-taping because of inappropriate wording, provided the IRB reviews the final audio/video tape.)

N/A

- Multi-Site Data Management
  - Check all applicable boxes below.
    - ☐ NCH will SEND data to other sites
    - ☐ NCH will RECEIVE data from other sites
  - Describe the procedures for maintenance or confidentiality of data at non-NCH sites.
    - Where and how data or specimens will be stored?
    - How long the data or specimens will be stored?
    - Who will have access to the data or specimens?
    - Who is responsible for receipt or transmission of the data of specimens?
    - How data specimens will be transported?

N/A

☐ NCH investigator **IS** the LEAD investigator in the study.
☐ NCH **IS NOT** the LEAD investigator in the study. No further information needed in this section.

- Review "WORKSHEET: Communication and Responsibilities (HRP-830)"
- Describe the processes for communication among sites to conduct the study in accordance with applicable federal regulations and local laws.
- Describe the method for reporting the following:
  - Problems (inclusive of reportable events)
  - Non-compliance with the study protocol of applicable requirements
  - Interim results
  - The closure of the study

.

N/A