Scenario B. Non-Exempt Human Subjects Research

Criteria

[Human Subjects Research](#Human_Subjects_Defs_Human) Yes

[Exemption Claimed](#Human_Subjects_Exemption_Cat) No

[Clinical Trial](#Human_Subjects_Defs_ClinicalTrial) No

[NIH-Defined Phase III Clinical Trial](#Human_Subjects_Defs_NIH_PhaseIIIl) No

Protections of Human Subjects

Inclusion of Women and Minorities

Targeted/Planned Enrollment Table(s)

Inclusion of Children

**Protections of Human Subjects**

SF 424 Instructions

[**https://grants.nih.gov/grants/how-to-apply-application-guide/forms-d/supplemental-instructions-forms-d.pdf**](https://grants.nih.gov/grants/how-to-apply-application-guide/forms-d/supplemental-instructions-forms-d.pdf)

a. Human Subjects Involvement, Characteristics, and Design

* Describe the proposed involvement of human subjects in the work outlined in the Research Strategy section.
* Describe and justify the characteristics of the subject population, including their anticipated number, age range, and health status if relevant.
* Describe and justify the sampling plan, as well as the recruitment and retention strategies and the criteria for inclusion or exclusion of any subpopulation.
* Explain the rationale for the involvement of special vulnerable populations, such as fetuses, neonates, pregnant women, children, prisoners, institutionalized individuals, or others who may be considered vulnerable populations. Note that 'prisoners' includes all subjects involuntarily incarcerated (for example, in detention centers) as well as subjects who become incarcerated after the study begins.
* If relevant to the proposed research, describe procedures for assignment to a study group. As related to human subjects protection, describe and justify the selection of an intervention’s dose, frequency, and administration.
* List any collaborating sites where human subjects research will be performed, and describe the role of those sites and collaborating investigators in performing the proposed research. Explain how data from the site(s) will be obtained, managed, and protected.

b. Sources of Materials

* Describe the research material obtained from living individuals in the form of specimens, records, or data.
* Describe any data that will be collected from human subjects for the project(s) described in the application.
* Indicate who will have access to individually identifiable private information about human subjects.
* Provide information about how the specimens, records, and/or data are collected, managed, and protected as well as whether material or data that include individually identifiable private information will be collected specifically for the proposed research project.

c. Potential Risks

* Describe the potential risks to subjects (physical, psychological, financial, legal, or other), and assess their likelihood and seriousness to the human subjects.
* Where appropriate, describe alternative treatments and procedures, including the risks and potential benefits of the alternative treatments and procedures, to participants in the proposed research. When alternative treatments or procedures are possible, the rationale for the proposed approach should be clear.

### 4.1.2 Adequacy of Protection Against Risks

a. Recruitment and Informed Consent

* Describe plans for the recruitment of subjects (where appropriate) and the process for obtaining informed consent. If the proposed studies will include children, describe the process for meeting requirements for parental permission and child assent.
* Include a description of the circumstances under which consent will be sought and obtained, who will seek it, the nature of the information to be provided to prospective subjects, and the method of documenting consent. When appropriate, describe how potential adult subjects’ capacity to consent will be determined and plans for obtaining consent from a legally authorized representative for adult subjects not able to consent.
* If a waiver of some or all of the elements of informed consent will be sought, provide justification for the waiver. Informed consent document(s) need not be submitted to the PHS agencies unless requested

b. Protections Against Risk

* Describe planned procedures for protecting against or minimizing potential risks, including risks to privacy of individuals or confidentiality of data, and assess their likely effectiveness.
* Research involving vulnerable populations, as described in the DHHS regulations, Subparts B-D must include additional protections. Refer to DHHS regulations, and OHRP guidance:
* Additional Protections for Pregnant Women, Human Fetuses and Neonates: <http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm#subpartb>
* Additional Protections for Prisoners: <http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm#subpartc>
* OHRP Subpart C Guidance: <http://www.hhs.gov/ohrp/policy/index.html#prisoners>
* Additional Protections for Children: <http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html#subpartd>
* OHRP Subpart D Guidance: <http://www.hhs.gov/ohrp/policy/index.html#children>
* Where appropriate, discuss plans for ensuring necessary medical or professional intervention in the event of adverse effects to the subjects. Studies that involve clinical trials (see definition of “clinical trial” under Part III Section 3) must include a separate attachment describing the plan for data and safety monitoring of the clinical trials and adverse event reporting to the IRB, the DSMB (if one has been established for the trial), the NIH and others, as appropriate, to ensure the safety of subjects.
* Where appropriate, describe plans for handling incidental findings that may be uncovered as a result of the research, such as incidental findings from research imaging, results of screening tests, or misattributed paternity.

NOTE: Test articles (investigational new drugs, devices, or biologics) including test articles that will be used for purposes or administered by routes that have not been approved for general use by the Food and Supplemental Grant Application Instructions II-10 Drug Administration (FDA) must be named. State whether the 30-day interval between submission of applicant certification to the FDA and its response has elapsed or has been waived and/or whether use of the test article has been withheld or restricted by the FDA, and/or the status of requests for an Investigational New Drug (IND) or Investigational Device Exemption (IDE) covering the proposed use of the test article in the Research Plan.

### 4.1.3 Potential Benefits of the Proposed Research to Human Subjects and Others

* Discuss the potential benefits of the research to research participants and others.
* Discuss why the risks to subjects are reasonable in relation to the anticipated benefits to research participants and others.
* Please note that financial compensation of subjects should not be presented as a benefit of participation in research.

### 4.1.4 Importance of the Knowledge to be Gained

* Discuss the importance of the knowledge gained or to be gained as a result of the proposed research.
* Discuss why the risks to subjects are reasonable in relation to the importance of the knowledge that reasonably may be expected to result.

**Examples**

**From a U01 Grant**

**Protection of Human Subjects**

During our participation in the collaborative studies referenced in this application and already ongoing, we will follow all protocols in order to decrease risk and protect the well being of our subjects. Because this application addresses a large number of trials, we will focus this section on the protection of human subjects measures for our pilot study.

**“A Prospective Longitudinal Study of Children with CF and Liver disease using MRI/MRS”**

Human Subject Involvement and Characteristics: The study population consists of children age 2-8 years at initial enrollment, both male and female. All racial and ethnic groups will be included and the subjects will consist of children with the diagnosis of cystic fibrosis but not necessarily liver involvement.

Sources of material: Information and samples will be collected during routine clinical care and they will not be restricted in any type of treatment. They will undergo an annual MRI/MRS and this data will be available both for their clinical care and for the prospective database.

**Inclusion Criteria**

Positive sweat test confirming cystic fibrosis

 Age 2 to 8 years old at entry

 Normal BUN and creatinine within past 6 months

**Exclusion Criteria**

 Established cirrhosis

 Listing for Liver Transplant or past liver transplant

 Renal insufficiency or failure

**Potential Risks:**

For the observational portions of the study, in general, there are no adverse events that can be attributed to it except at the time of blood draws. There are minimal physical and psychological risks from being in this study. For the *database study*, the risks of venipuncture at the time of the blood draws are pain, bruising or superficial phlebitis. The risks of genetic information being revealed by any future investigations in the Consortium are very slight since the blood samples will be de-identified prior to being deposited in the repository; that is only a research study number will be included in the database and all dates will be converted into ages by the DCC prior to dissemination to the repository or to any laboratory conducting genetic studies.

For the MRI/MRS portions of the study, the subject may receive contrast solution (dye) as part of the MRI exam. This requires placement of an IV (intravenous) line in the arm. This may cause some discomfort or bruising at the insertion site. There is a minimal risk of local infection, which can be treated with oral antibiotics.

Contrast Agent: Commonly occurring side effects for contrast solutions are vomiting, headaches, dizziness, flushing (warm sensation in the body), and taste sensations. One of the more severe, but extremely rare, risks is that of anaphylaxis (a severe allergic reaction that can cause breathing difficulties and /or low blood pressure). There is always the risk of uncommon or previously unknown side effects. There is the potential for peripheral nerve (nerves in the arms, hands, legs, and feet) to be stimulated by the stronger magnet system, which could result in a tingling sensation, warmth or even pain. You will be in constant communication with the technologist, who will immediately stop the scanner if you have such sensations or concerns.

The contrast for MRIs could cause a serious skin reaction. The risk for this is very low risk. This usually happens in patients who have kidney disease. For this reason, patients with renal insufficiency or renal failure will be excluded.

**Recruitment and Informed Consent**:

Patients will be recruited at our center through contact initially by an informational letter and then invitation at the time of a clinic visit. Because the MRI will need to be scheduled, in order to make it more convenient for patients, we will give them the opportunity to schedule it on the same day as their routine clinic visit. Informed consent will be obtained prior to any study procedures. A common template for the informed consent form will be used by all of the centers, modifying the content or format as necessary to meet the requirements of their respective institutional human subjects committees. The subject will retain a signed consent form; one will be retained for the subject’s chart; and one will be included in the research records.

**Protections against risk**

Whenever possible, blood samples will be obtained in conjunction with clinical samples. When not possible, the bruising at the time of blood draws may be attributable to this study. If an MRI is clinically indicated an obtained, this will be used as their annual MRI so as not to put the family or child through additional physical or psychologic stress. Sedation at the time of MRI is the primary risk, and this will be minimized by keeping the MRI as short as possible and using the minimal amount of sedation required. A rare but serious adverse skin reaction can be seen with gadolinium but this only occurs in the setting of renal dysfunction. A normal creatinine and BUN within the past 6 months and no history of renal disease will be required prior to MRI in order to assure normal renal function and decrease this risk.

**Potential Benefits of the Proposed Research**

Each subject may not benefit individually from this research. The MRI/MRS information will be used to correlate clinical outcomes with measurements and there may not be a direct benefit. All MRs will be evaluated clinically as well, so as not to miss a clinically important imaging finding and this could provide some benefit to subjects. In addition, at the conclusion of this study, if our hypothesis is correct we may have relevant treatment options for these patients to improve their liver disease.

**Importance of the Knowledge to be Gained**

At this time, very little is known about the clinical predictors and correlations with cystic fibrosis liver disease despite the fact that it is a leading cause of mortality. Because repeat liver biopsy is unsafe and has inherent accuracy problems, treatment trials of CF liver disease are difficult if not impossible. The establishment of clinical predictors of significant liver disease will allow us to focus treatment efforts on those patients who will have significant disease. MRI/MRS will also allow us to track treatment effects more accurately than liver biopsy and liver enzymes.

***Data Safety Monitoring Board***

The National Institutes of Health have set up a Data Safety Monitoring Board (DSMB) to oversee this study. The Data and Safety Monitoring Board (DSMB) will act in an advisory capacity to NIDDK to monitor patient safety and evaluate the ability of the ChiLDREN to achieve its research goals. Members of the DSMB are independent of the study investigators and represent disciplines related to liver disease, biostatistics and

epidemiology, as well as possibly having a lay member. The DSMB will meet every six months or more frequently if requested by the Chair of the DSMB or the NIDDK Program Director, either in person or by teleconference.

**From a K23 Application**

 **Risks to Human Subjects**

**a.**

***Human Subjects Involvement, Characteristics, and Design*.**

As part of the proposed research strategy, human subjects with mild/moderate HA will be observed while they undergo surgical interventions. Clinical data through subject interview and medical record review and blood samples for laboratory studies will be collected. The surgical procedure and its management will be dictated by the medical team and will not be altered by the study.

Sample size was estimated based on a retrospective cohort study published by Eckhardt et al.17 In this study, a total of 17% of patients having surgery as their first intensive fVIII exposure developed an inhibitor; 50% while receiving continuous infusion and 6.5% while receiving a bolus injection. Inhibitors occurred most commonly in subjects with a specific fVIII mutation (R593C). This mutation is common in the Netherlands where this study was conducted, likely as the result of a founder effect. Overall, those with the R593C fVIII mutation developed an inhibitor 50% of the time. In those without R593C, an inhibitor developed in 25% of those that received a continuous infusion. Since the R593C missense mutation is not likely to be as common in a study population from the United States, this study will be powered to detect a conservatively estimated difference of 0.20. Since this is an observational study, the proportion of subjects receiving fVIII replacement by continuous infusion or bolus injection will not be set. With a sample size of 140 and alpha 0.05, the power to detect a 0.20 difference in the proportion of subjects developing a fVIII inhibitor ranges from 0.80 to 0.93 depending on the proportion of subjects receiving a continuous infusion (0.25-0.75) (Table 1). We anticipate having 10 participating sites enroll approximately 10-20 subjects each over a 3 year period for a total enrollment of 140 subjects (Table 2). Given the short follow-up period, we do not anticipate significant subject drop out. During the preceding year, 57 surgeries occurred in potentially eligible subjects at the 10 participating sites. Six of the ten sites use both continuous infusion and bolus injection (encompassing 40 surgeries during the past year), whereas 4 sites prefer to use bolus injection only (encompassing 17 surgeries during the past year).

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| Table 1. Sample size calculations **SAMPLE SIZE CONTINUOUS INFUSION** **P (INHIBITOR) =0.25**  | **SAMPLE SIZE** **BOLUS INJECTION** **P (INHIBITOR)=0.05**  | **POWER**  |
| 35  | 105  | 0.86  |
| 47  | 93  | 0.93  |
| 56  | 84  | 0.93  |
| 70  | 70  | 0.90  |
| 84  | 56  | 0.92  |
| 93  | 47  | 0.90  |
| 105  | 35  | 0.80  |

C:\Users\jkenny2\AppData\Local\Microsoft\Windows\Temporary Internet Files\Content.Outlook\1XPE3DXT\HumanSubjects.doc - Human\_Subjects\_Research\_RisksToSub**Inclusion of Women and Minorities**

SF 424 Instructions

Scientific Review Groups will assess each application as being acceptable or unacceptable with regard to the inclusion of women and minorities in clinical research.

In this section of the Research Plan, address, at a minimum, the following four points:

1. Describe the planned distribution of subjects by sex/gender, race, and ethnicity for each proposed study and complete the format in the PHS Inclusion Enrollment Report. Instructions for completing this form are in the General Application Guide for NIH and Other PHS Agencies Section G.500, and below in Part II Section 4.3 of these Supplemental Instructions.
2. Describe the subject selection criteria and rationale for selection of sex/gender, racial, and ethnic group members in terms of the scientific objectives and proposed study design. The description may include, but is not limited to, information on the population characteristics of the disease or condition under study.
3. Provide a compelling rationale for proposed sample specifically addressing exclusion of any sex/gender, racial, or ethnic group that comprises the population under study.
4. Describe proposed outreach programs for recruiting sex/gender, racial, and ethnic group members as subjects. This is particularly important if difficulty recruiting certain groups is anticipated.

Exclusion of gender or minorities must be justified. See below for acceptable justifications for this.

A. One gender:

1. One gender is excluded from the study because:

* inclusion of these individuals would be inappropriate with respect to their health;
* the research question addressed is relevant to only one gender;
* evidence from prior research strongly demonstrates no difference between genders; or
* sufficient data already exist with regard to the outcome of comparable studies in the excluded gender, and duplication is not needed in this study.

2. One gender is excluded or severely limited because the purpose of the research constrains the applicant's selection of study subjects by gender (e.g., uniquely valuable stored specimens or existing datasets are single gender; very small numbers of subjects are involved; or overriding factors dictate selection of subjects, such as matching of transplant recipients, or availability of rare surgical specimens).

3. Gender representation of specimens or existing datasets cannot be accurately determined (e.g., pooled blood samples, stored specimens, or data-sets with incomplete gender documentation are used), and this does not compromise the scientific objectives of the research.

B. Minority groups or subgroups:

1. Some or all minority groups or subgroups are excluded from the study because:

* inclusion of these individuals would be inappropriate with respect to their health;
* the research question addressed is relevant to only one racial or ethnic group;
* evidence from prior research strongly demonstrates no differences between racial or ethnic groups on the outcome variables;
* a single minority group study is proposed to fill a research gap; or
* sufficient data already exists with regard to the outcome of comparable studies in the excluded racial or ethnic groups and duplication is not needed in this study.

2. Some minority groups or subgroups are excluded or poorly represented because the geographical location of the study has only limited numbers of these minority groups who would be eligible for the study, and the investigator has satisfactorily addressed this issue in terms of:

* the size of the study;
* the relevant characteristics of the disease, disorder or condition; or
* the feasibility of making a collaboration or consortium or other arrangements to include representation.

3. Some minority groups or subgroups are excluded or poorly represented because the purpose of the research constrains the applicant's selection of study subjects by race or ethnicity (e.g., uniquely valuable cohorts, stored specimens or existing datasets are of limited minority representation, very small numbers of subjects are involved, or overriding factors dictate selection of subjects, such as matching of transplant recipients or availability of rare surgical specimens).

4. Racial or ethnic origin of specimens or existing datasets cannot be accurately determined (e.g., pooled blood samples, stored specimens or data sets with incomplete racial or ethnic documentation are used) and this does not compromise the scientific objectives of the research.

**Examples**

**From a U01 Grant**

**Inclusion of Women and Minorities**

Targeted/planned enrollment will include women and minorities. We anticipate that our study population will have more caucasians because of the distribution of CF, however we have a black patient tranplanted for CF so it is entirely possible that we will have some black patients as well.

**From a K23 Application**

 ***Inclusion of Women and Minorities***

The research question proposed in this application pertains to hemophilia A, an X-linked disorder that affects males. Therefore women will not be included in the research. Although some women that are carriers of hemophilia A may have low levels of fVIII that necessitate treatment with fVIII at the time of surgery, the number of women carriers that could be enrolled in this study would be very low and not facilitate any evaluation of the influence of gender on outcomes.

All races and ethnicities will be included. Hemophilia affects all racial and ethnic groups. Since 10 treatment centers will be participating and representing nearly every region of the United States, we expect to recruit subjects that are representative of the general population. Spanish consents will be made available to facilitate enrollment of subjects with Hispanic ethnicity.

**PHS Inclusion Enrollment Report(s) for Sex/Gender, Race and Ethnicity**

* <http://grants.nih.gov/grants/how-to-apply-application-guide/forms-d/general/g.500-phs-inclusion-enrollment-report.htm>
* <https://grants.nih.gov/grants/how-to-apply-application-guide/forms-d/supplemental-instructions-forms-d.pdf#4_3_instructions_for_completing>

The PHS Inclusion Enrollment Report form is used for all applications involving NIH-defined clinical research. This form is used to report both planned and cumulative (or actual) enrollment, and describes the sex/gender, race, and ethnicity of the study participants.

**Inclusion of Children**

SF 424 Instructions

**For the purpose of implementing these guidelines, a child is defined as an individual under the age of 18 years (for additional information see** [**http://grants.nih.gov/grants/funding/children/children.htm**](http://grants.nih.gov/grants/funding/children/children.htm)

It is important to provide a detailed plan of who will be included (and/or excluded) based on age. Details about why the individuals in the given age/age range are the appropriate individuals to accomplish the scientific goals of the study should be provided.

Instructions for this item of the Research Plan **including addressing the following points:**

* Describe the age(s) or age range of all individuals to be included in the proposed study.
* Specifically discuss whether children under the age of 18 (as a whole or a subset of individuals under 18) will be included or excluded.
* The description of the plan should include a rationale for selecting a specific age range of children.
* The plan also must include a description of the expertise of the investigative team for working with children at the ages included, of the appropriateness of the available facilities to accommodate the children, and the inclusion of a sufficient number of children to contribute to a meaningful analysis relative to the purpose of the study.
* When children are involved in research, the Additional Protections for Children Involved as Subjects in Research (45 CFR part 46 Subpart D) apply and must be addressed under the Protections Against Risk subheading (4.1.2.b).

**Examples**

**From a K23 Application**

 ***Inclusion of Children***

The proposed research includes children. No specific age range has been pre-defined, however; for safety with respect to the volume of blood to be drawn at each visit, subjects need to weigh > 22.5 kg. Therefore it is unlikely that subjects will be less than 4 years of age (95th percentile for weight at age 4 is 20 kg). Since it is an observational study, the care of the children will be done by pediatricians trained to care for children with hemophilia at institutions that care for children routinely. Parental consent will be obtained and procedures for assent at each institution will be followed. All participating sites, except University of Minnesota care for patients of all ages and have a multidisciplinary staff to care for both children and adults. Although at these centers children may represent approximately half of all potential subjects, children are less likely to need surgery; therefore we anticipate that they would encompass approximately 25% of the enrolled subjects.