CLINICAL & TRANSLATIONAL RESEARCH CENTER PROTOCOL SUBMISSION INFORMATION

For your project, the CTRC requires the following information to be provided. This is above and beyond the current requirements for the Institutional Review Board (IRB) and aligns us with the requirements of the NIH, which is where we want to be with all studies. This information may be contained in an NIH grant application, if you have one, or in your clinical protocol (and can be cut and pasted into the addendum). For your project, please attach an addendum addressing the following points:

HUMAN SUBJECTS' ADDENDUM

1. RISKS TO THE SUBJECTS

a. ***Human Subjects Involvement and Characteristics***

- Describe the proposed involvement of human subjects in the work outlined in the Research Design and Methods section.
- Describe the characteristics of the subject population, including their anticipated number, age range, and health status.
- Identify the criteria for inclusion or exclusion of any subpopulation.
- Explain the rationale for the involvement of special classes of subjects, 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.
- List any collaborating sites where human subjects research will be performed, and describe the role of those sites in performing the proposed research.

b. ***Sources of Materials***

- Describe the research material obtained from living human subjects in the form of specimens, records, or data.
- Describe any data that will be recorded on the human subjects involved in the project.
- Describe the linkages to subjects, and indicate who will have access to subject identities.
- Provide information about how the specimens, records, or data are collected and whether material or data will be collected specifically for your proposed research project.

c. ***Potential Risks***

- Describe the potential risks to subjects (physical, psychological, social, legal, or other), and assess their likelihood and seriousness to the subjects.
- Where appropriate, describe alternative treatments and procedures, including the risks and benefits of the alternative treatments and procedures to participants in the proposed research.

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. Informed consent document(s) need not be submitted to the PHS agencies unless requested.

b. ***Protection Against Risk***

- Describe planned procedures for protecting against or minimizing potential risks, including risks to confidentiality, and assess their likely effectiveness.

- 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 (biomedical and behavioral intervention studies) must include a description of the plan for data and safety monitoring of the research and adverse event reporting to ensure the safety of subjects.

3. POTENTIAL BENEFITS OF THE PROPOSED RESEARCH TO THE SUBJECTS AND OTHERS

- Discuss the potential benefits of the research to the subjects and others.

- Discuss why the risks to subjects are reasonable in relation to the anticipated benefits to subjects and others.

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.

NOTE: Test articles (investigational new drugs, devices, or biologicals) 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 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 Food and Drug Administration, and/or the status of requests for an IND or IDE covering the proposed use of the test article in the research plan.

5. DATA AND SAFETY MONITORING PLAN

- Provide a general description of a monitoring plan that you plan to establish as the overall framework for data and safety monitoring. Describe the entity that will be responsible for monitoring and the process by which Adverse Events (AEs) and unanticipated problems will be reported to the Institutional Review Board (IRB), the funding I/C, the NIH Office of Biotechnology Activities (OBA), if applicable, and the Food and Drug Administration (FDA), if applicable, in accordance with Investigational New Drug (IND) or Investigational Device Exemption (IDE) regulations. Be succinct. Contact the FDA (http://www.fda.gov/) and also see the following

websites for more information related to IND and IDE requirements:
http://www.access.gpo.gov/nara/cfr/waisidx_01/21cfr312_01.html (IND)
http://www.access.gpo.gov/nara/cfr/waisidx_01/21cfr812_01.html (IDE)

and for CCHMC guidelines, follow this link from the ORCRA watercooler: Data and Safety Monitoring in Research

Please be explicit that both Adverse Events (AEs) and unanticipated problems will be reported to the CCHMC IRB.

- The DSMP must include a description of how often the monitoring is taking place. The frequency of monitoring will depend on potential risks, complexity, and the nature of the trial; therefore, a number of options for monitoring trials are available. These can include, but are not limited to, monitoring by a:
    a. Principal Investigator (required)
    b. Independent individual/Safety Officer
    c. Designated medical monitor
    d. Internal Committee or Board with explicit guidelines
    e. Data and Safety Monitoring Board (DSMB). NIH specifically requires the establishment of Data and Safety Monitoring Boards (DSMBs) for *multi-site* clinical trials involving interventions that entail potential *risk* to the participants, and generally for Phase III clinical trails. Although Phase I and Phase II clinical trials may also use DSMBs, smaller clinical trials may not require this oversight format, and alternative monitoring plans may be appropriate. **Please furnish a copy of the charter.**
    f. Institutional Review Board (IRB - required). The planned frequency of review by the indicated person or group should be specified in the DSMP.
- A detailed Data and Safety Monitoring Plan must be submitted to the applicant's IRB and subsequently to the funding IC for approval prior to the accrual of human subjects (http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-038.html). For additional guidance on creating this Plan, see the above references.

6. INCLUSION OF WOMEN AND MINORITIES

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

1. The targeted/planned distribution of subjects by sex/gender and racial/ethnic groups for each proposed study or protocol using the format in the Targeted/Planned Enrollment Table. (Instructions for completing this table are provided below.) If you are using existing specimens and/or data that does not meet the criteria for Exemption 4 and you do not have access to information on the distribution of women and minorities, so state and explain the impact on the goals of the research as part of the rationale that inclusion is inappropriate (item 3 below). Alternatively, you may describe the women and minority composition of the population base from whom the specimens and/or data will be obtained. Include the Targeted/Planned Enrollment Table (MS Word or PDF) in this section.

2. A description of the subject selection criteria and rationale for selection of sex/gender and racial/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. A compelling rationale for proposed exclusion of any sex/gender or racial/ethnic group (see examples below).

4. A description of proposed outreach programs for recruiting sex/gender and racial/ethnic group members as subjects.

Examples of acceptable justifications for exclusion of:

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;
    - 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;
    - 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;
    - 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.

7. INCLUSION OF CHILDREN

- For the purpose of implementing these guidelines, a ***child*** is defined as an individual under the age of 21 years (for additional information see http://grants.nih.gov/grants/funding/children/children.htm and http://grants.nih.gov/grants/guide/notice-files/not98-024.html).

- Provide either a description of the plans to include children or, if children will be excluded from the proposed research, application, or proposal, then you must present an acceptable justification (see below) for the exclusion.

- If children are included, 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 dealing 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.

- Scientific Review Groups will assess each application as being "acceptable" or "unacceptable" with regard to the age-appropriate inclusion or exclusion of children in the research project.

- 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 in the “Human Subjects Research and Protection from Risks” subheading.

Justifications for Exclusion of Children:

For the purposes of this policy, all individuals under 21 are considered children; however, exclusion of any specific age group, such as individuals under 18, should be justified in this section.

It is expected that children will be included in all clinical research unless one or more of the following exclusionary circumstances can be fully justified:

1. The research topic to be studied is not relevant to children.

2. There are laws or regulations barring the inclusion of children in the research.

3. The knowledge being sought in the research is already available for children or will be obtained from another ongoing study, and an additional study will be needlessly redundant. Documentation of other studies justifying the exclusions should be provided. NIH program staff can be contacted for guidance on this issue if the information is not readily available.

4. A separate, age-specific study in children is warranted and preferable. Examples include:

   a. The condition is relatively rare in children, as compared to adults (in that extraordinary effort would be needed to include children, although in rare diseases or disorders where the applicant has made a particular effort to assemble an adult population, the same effort would be expected to assemble a similar child population with the rare condition); or

   b. The number of children is limited because the majority are already accessed by a nationwide pediatric disease research network; or

   c. Issues of study design preclude direct applicability of hypotheses and/or interventions to both adults and children (including different cognitive, developmental, or disease stages or different

age-related metabolic processes). While this situation may represent a justification for excluding children in some instances, consideration should be given to taking these differences into account in the study design and expanding the hypotheses tested, or the interventions planned, to allow inclusion of children rather than excluding them.

5. Insufficient data are available in adults to judge potential risk in children (in which case one of the research objectives could be to obtain sufficient adult data to make this judgment). Although children usually should not be the initial group to be involved in research studies, in some instances, the nature and seriousness of the illness may warrant their participation earlier based on careful risk and benefit analysis.

6. Study designs are aimed at collecting additional data on pre-enrolled adult study subjects (e.g., longitudinal follow-up studies that did not include data on children).

7. Other special cases can be justified by the investigator and found acceptable to the review group and the Institute Director.

Targeted/Planned Enrollment Table

Provide a description of the proposed study population in terms of gender and racial/ethnic group, giving an estimated percentage of each, utilizing the following table. The investigator must explain what outreach program is being implemented to ensure appropriate recruitment. If women, children and minorities are not to be included in your project, a clear rationale for their exclusion must be provided.

***Gender**: Male*
Female

***Ethnicity:** Hispanic or Latino*
Not Hispanic or Latino

***Race:** American Indian or Alaska Native*
Asian
Native Hawaiian/Other Pacific Islander
Black or African American
White

Total Planned Enrollment:

TARGETED/PLANNED ENROLLMENT: Number of Subjects			
Ethnic Category	**Sex/Gender**		
	Females	**Males**	**Total**
Hispanic or Latino			
Not Hispanic or Latino			
Ethnic Category: Total of All Subjects *			
Racial Categories			
American Indian/Alaska Native			
Asian			
Native Hawaiian or Other Pacific Islander			
Black or African American			
White			
Racial Categories: Total of All Subjects *			

* The “Ethnic Category: Total of All Subjects” must be equal to the “Racial Categories: Total of All Subjects”.

EXAMPLE OF DATA AND SAFETY MONITORING PLAN **(Taken from one of Dr. Heubi's Protocols)**

Data and Safety Monitoring Board (Not necessary for all protocols):

A Drug Safety Monitoring Board (DSMB) will be assembled which will include Dr. Richard Wenstrup, a pediatric geneticist with experience using alendronate for treatment of adults with Gaucher Disease, Dr. Heidi Kalkwarf, an Assistant Professor of Pediatrics with extensive experience with bone mineral metabolism and imaging techniques and Dr. Judy Bean, a biostatistician. Reports of adverse events will be provided to this group on an ongoing basis and they will meet every 6 months to assess progress of the proposal as well as adverse events. This group will assess adverse events and evaluate trends particularly as they relate to gastrointestinal symptoms since this is the area in which the highest risk of adverse events is likely to be seen. Should a trend in increased adverse events be recognized in the area of GI symptoms, the DSMB will meet and review them and make recommendations about modifying or continuing the study to prevent or reduce the frequency of these effects. Should a large statistically significant difference of improvement become apparent between the risedronate and placebo group, and this is judged by DSMB to be clinically significant, the committee will stop the study on ethical grounds Likewise, if the DSMB determines that one group has a significantly higher incidence of adverse effects, the study will be terminated early.

ATTACHMENT

RACIAL/ETHNIC COMPOSITION OF POPULATIONS BY CATCHMENT AREAS

(Shown as percent of total population)

2010 Census

Race & Ethnicity (%)	US	Ohio	Hamilton County	Greater Cincinnati	Cincinnati	CCHMC
White	72.4	82.7	68.8	82.9	49.3	62.0
African-American	12.6	12.2	25.7	12.0	44.8	18.4
American Indian/Alaskan Native	0.9	0.2	0.2	0.2	0.3	0.1
Asian	4.8	1.7	2.0	1.9	1.8	1.0
Native Hawaiian/Other Pacific Islander	0.2	0.0	0.0	0.1	0.1	0.1
Other	6.2	1.1	1.2	1.1	1.2	18.4
Two or More Races/Unknown	2.9	2.1	2.1	1.8	2.5	-
Hispanic or Latino	16.3	3.1	2.6	2.6	2.8	-
Non-Hispanic or Latino	83.7	96.9	97.4	97.4	97.2	-
Gender (%)						
Male	49.2	49.0	48.0	48.9	48.0	49.0
Female	50.8	51.0	52.0	51.1	52.0	51.0

Notes: CCHMC & UC collects data on FY basis.

CCHMC may start collecting hispanic/nonhispanic data in FY 12

Greater Cincinnati Area (Cincinnati Metropolitan Statistical Area or MSA) as defined by Census.gov: Boone, Kenton, Campbell, Gallatin, Grant and Pendleton counties in Kentucky; Dearborn and Ohio counties in Indiana; Brown, Butler, Clermont, Hamilton and Warren counties in Ohio.

Sources: US 2010 Census (internet site), Ohio 2010 Census (Internet site), Cincinnati Chamber of Commerce, CCHMC Office of Business & Planning