Note to investigators:

The following protocol template was derived from Good Clinical Practice (GCP) Guidelines – an international ethical and scientific quality standard for designing, conducting, recording, and reporting trials that involve the participation of human subjects. It is intended to provide a basic framework for organizing your research plan.

The complete GCP guidelines can be found at: http://www.fda.gov/oc/gcp/guidance.html Scroll down the page to find: ICH E6: Good Clinical Practice: Consolidated Guidance. When you open the document – the cover page will say “Guidance for Industry”. Do not be confused by this. Application of GCP standards to clinical research is not limited to research conducted by (or for) industry.
PROTOCOL

A Registry of Patients
with
Primary Immunodeficiency Disorders

Version: 1.04F

August 2012
GENERAL INFORMATION

Name and address of the sponsor of the study
United States Immunodeficiency Network (USIDNET)
40 West Chesapeake Avenue, Suite 308 Towson, MD 21204

Name and address of the person authorized to sign the protocol and amendments
Ramsay Fuleihan, M.D.
United States Immunodeficiency Network (USIDNET)
40 West Chesapeake Avenue, Suite 308 Towson, MD 21204

Name and address of study monitor
Tiffany Sweetwine Project/Study Coordinator
United States Immunodeficiency Network (USIDNET)
40 West Chesapeake Avenue, Suite 308 Towson, MD 21204

Name, title, address and telephone number(s) of the medical expert for the trial
Ramsay L. Fuleihan, M.D.
United States Immunodeficiency Network (USIDNET)
40 West Chesapeake Avenue, Suite 308 Towson, MD 21204
443.632.2556
773.327.1701
TABLE OF CONTENTS

1.0 BACKGROUND .................................................................................................................. 8
  1.1 INVESTIGATIONAL AGENT .......................................................................................... 10
  1.2 PRE-REGISTRY DATA ................................................................................................. 10
  1.3 RISK/BENEFITS ........................................................................................................ 11
  1.4 PURPOSE ..................................................................................................................... 11
  1.5 TRIAL CONDUCT ........................................................................................................ 11
  1.6 POPULATION ............................................................................................................... 11
  1.7 LITERATURE ............................................................................................................... 12

2.0 TRIAL OBJECTIVES .......................................................................................................... 12

3.0 TRIAL DESIGN .................................................................................................................. 12
  3.1 USIDNETS COLLABORATION WITH THE CENTER FOR INTERNATIONAL BLOOD AND
     MARROW TRANSPLANT RESEARCH (CIBMTR) ............................................................. 14
  3.2 PRIMARY STUDY ENDPOINTS/SECONDARY ENDPOINTS .................................. 15
  3.3 DURATION ................................................................................................................... 15
  3.4 DISCONTINUATION ..................................................................................................... 15
  3.5 DATA IDENTIFICATION .............................................................................................. 15

4.0 SELECTION AND WITHDRAWAL OF SUBJECTS ............................................................ 15
  4.1 INCLUSION CRITERIA ................................................................................................. 15
  4.2 EXCLUSION CRITERIA ............................................................................................... 16
  4.3 SUBJECT WITHDRAWAL ........................................................................................... 16
  4.4 ENROLLMENT/RECRUITMENT METHODS ................................................................. 16

5.0 ASSESSMENT OF SAFETY .............................................................................................. 16
  5.1 ADVERSE EVENT REPORTING .................................................................................. 16
  5.2 DEFINITIONS ............................................................................................................. 17
  5.3 ADVERSE EVENT FOLLOW-UP ................................................................................ 17

6.0 STATISTICAL METHODS ................................................................................................ 17

Page 4 of 32
6.1 DATA MANAGEMENT AND STATISTICAL ANALYSIS .......................................................... 17
6.2 DEVIATION REPORTING ................................................................................................. 18

7.0 QUALITY CONTROL AND QUALITY ASSURANCE .................................................. 19

8.0 ETHICAL CONSIDERATIONS ....................................................................................... 19

9.0 DATA HANDLING AND RECORD KEEPING .............................................................. 19

10.0 FINANCE AND INSURANCE ...................................................................................... 20

APPENDIX

1.0 CORE FORM .................................................................................................................. 21
**List of Abbreviations**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>AE</td>
<td>Adverse Event</td>
</tr>
<tr>
<td>CFR</td>
<td>Code of Federal Regulations</td>
</tr>
<tr>
<td>CGD</td>
<td>Chronic granulomatous disease</td>
</tr>
<tr>
<td>CIBMTR</td>
<td>Center for International Blood and Marrow Transplant Research</td>
</tr>
<tr>
<td>CRF</td>
<td>Case Report Form</td>
</tr>
<tr>
<td>CVD</td>
<td>Common variable immunodeficiency</td>
</tr>
<tr>
<td>DGS</td>
<td>DiGeorge syndrome</td>
</tr>
<tr>
<td>DHHS</td>
<td>Department of Health and Human Services</td>
</tr>
<tr>
<td>ESID</td>
<td>European Society for Immunodeficiency</td>
</tr>
<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
</tr>
<tr>
<td>FWA</td>
<td>Federal Wide Assurance</td>
</tr>
<tr>
<td>GCP</td>
<td>Good Clinical Practice</td>
</tr>
<tr>
<td>ICH</td>
<td>International Conference on Harmonisation</td>
</tr>
<tr>
<td>IDF</td>
<td>Immunodeficiency Foundation</td>
</tr>
<tr>
<td>IPEX</td>
<td>Immunodysregulation, Polyendocrinopathy, Enteropathy, X linked (IPEX) Syndrome</td>
</tr>
<tr>
<td>IRB</td>
<td>Institutional Review Board</td>
</tr>
<tr>
<td>LAD</td>
<td>Leukocyte adhesion deficiency</td>
</tr>
<tr>
<td>NIAID</td>
<td>National Institute of Allergy and Infectious Disease</td>
</tr>
<tr>
<td>NICHD</td>
<td>National Institute of Child Health and Human Development</td>
</tr>
<tr>
<td>NIH</td>
<td>National Institutes of Health</td>
</tr>
<tr>
<td>PHI</td>
<td>Personal Health Information</td>
</tr>
<tr>
<td>PI</td>
<td>Principal Investigator</td>
</tr>
<tr>
<td>Acronym</td>
<td>Description</td>
</tr>
<tr>
<td>---------</td>
<td>--------------------------------------</td>
</tr>
<tr>
<td>PIDD</td>
<td>Primary immune deficiency diseases</td>
</tr>
<tr>
<td>SCI</td>
<td>Severe combined immunodeficiency</td>
</tr>
<tr>
<td>USIDNET</td>
<td>United States Immunodeficiency Network</td>
</tr>
<tr>
<td>WAS</td>
<td>Wiskott – Aldrich syndrome</td>
</tr>
<tr>
<td>XHIGM</td>
<td>X-linked hyper IgM</td>
</tr>
<tr>
<td>XLA</td>
<td>X-linked agammaglobulinemia</td>
</tr>
</tbody>
</table>
1.0 Background

Primary immune deficiency diseases (PIDD) represent a class of disorders in which there is an intrinsic defect in the human immune system (rather than immune disorders that are secondary to infection, chemotherapy, or some other external agent). In some cases, the body fails to produce any or enough antibodies to fight infection. In other cases, the cellular defenses against infection fail to work properly. There are more than 80 different primary immune deficiency diseases currently recognized by the World Health Organization.

Medical recognition of primary immune deficiency disease is only fifty years old. Although these disorders may have existed in antiquity, it was not until the development of antibiotics that infections could be controlled long enough to recognize there was an underlying defect in the immune system. Also, the parallel development of gammaglobulin in World War II provided a replacement therapy for the antibody deficiency forms of immune deficiency.

Although primary immune deficiency diseases are often described as rare disorders, the true population prevalence of these diseases, either individually or in the aggregate, is not well established. The major health surveys conducted by the government in the United States, the National Health Interview Survey and the National Health and Nutrition Examination Survey, do not collect information on primary immune deficiency diseases. No comprehensive population survey has even been undertaken by the federal government to estimate the prevalence or the population characteristics of these diseases in the United States. Hence, although these diseases are clinically described in the medical literature, there is no comprehensive portrait available of the patient with primary immune deficiency disease.

In 1992 the National Institute of Allergy and Infectious Disease (NIAID) along with National Institutes of Health (NIH) contracted with the Immune Deficiency Foundation (IDF) to develop a Registry of patients with Chronic granulomatous disease (CGD). With the success of that initial registry, NIAID expanded the contract in 1998 to include eight different immunodeficiency disorders including (in addition to CGD): X-linked agammaglobulinemia (XLA), Common variable immunodeficiency (CVID), X-linked hyper IgM (X-HIGM), Leukocyte adhesion deficiency (LAD), Severe combined immunodeficiency (SCID), DiGeorge syndrome (DGS) and the Wiskott - Aldrich syndrome (WAS).

The Registry at that time was designed to be primarily a physician Registry with all contact between the Registry and the patient being carried out through the submitting physician. The Registry was de-identified with the patients assigned a unique code number. However, the patient’s initials and full date of birth were maintained in the record to help identify and eliminate duplicate registrations of the same patient by different physicians.
The contract for continuing operation of these Registries was included when NIAID and National Institute of Child Health and Human Development (NICHD) decided to change their mechanism for funding research in the primary immunodeficiency diseases and developed a consortium approach with a group of investigators banded together into an immunodeficiency disease network. The IDF assembled a group of prominent investigators in this field under the name United States Immunodeficiency Network (USIDNET) whose proposal was selected by NIAID for operation of the new research consortium that began in October 2003.

In 2006 the Steering Committee was developed and the duties of the committee members are to review and periodically update the data collection forms for their specific sub-Registry. The members act as an advisory committee to review and approve requests to use the data contained in that sub-Registry. The committee is also used to recruit colleagues to submit patients for the Registry and to develop research protocols that can be addressed using the Registry data or patient/physician list. Lastly, the committee is used to act as a publication committee to prepare periodic reports, or recruit authors to prepare reports, on the data being collected on specific disorders covered in their sub-Registry.

During the time the Steering Committee of the USIDNET was developed, the members decided that the future success of the Registry would be greatly enhanced if USIDNET joined forces with the European Society for Immunodeficiency (ESID) that has also established a Registry similarly containing about 1,500 patients. ESID has developed an electronic web-based data entry system that permits easy registration of patient data and the capacity to enter follow-up data on the patients over the course of time to assist determination of natural disease history and the outcome of various treatment procedures. Together these databases should provide the research community with a very powerful new tool to facilitate study of these individually rare disorders.

Disease Specific Working Groups (DSWGs): Taking a lead from the format of the ESID Patient Registry, the USIDNET has formed 11 Disease Specific Working Groups (DSWGs) to determine what data should be collected. DSWG members are composed of a Chair, a Co-chair and 2-5 other members who are especially interested in the individual defects. The USIDNET Disease Specific Working Groups are overseen by the Steering Committee. These committees designed the Core Case Report Form (for all PIDD patients) and separate disease specific forms. Using the Core Form, all data on patients are entered, even those with unknown defects, as these may become identifiable with time and this data will be preserved. These members realize the patient Registry is an amazing resource and are determined to help it grow. The members of the Disease Specific Working Groups have 6 main responsibilities:

1. Periodic data validations to identify any outliers or errors.
2. Review research protocols related to the disease.
4. Brainstorm for potential in-house research efforts that could be addressed by the Registry.
5. Review with the main centers for specific patient population and ensure that patient recruiting efforts have been maximized.
6. Review and revise the Disease Specific Working Group forms.

1.1 Investigational Agent
The Registry has no investigational agent.

1.2 Pre-Registry Data
Advances in the understanding of these disorders have been made by some institutions around the world. These institutions were able to accumulate patients to begin studying the range of symptoms that patients exhibit.

With the completion of the Human Genome Project, sudden increases of immunodeficiency disorders defined by mutations in unique genes were described. Researchers believe that there are a total of over 120 distinct gene defects. Although still individually rare, the aggregate frequency of patients presenting with a genetic disorder of immunity now approaches the frequency of patients with common genetic diseases such as, Cystic Fibrosis. It has been recognized that the definition of the phenotypic range of presentations of these multiple disorders, as well as their natural history, could be greatly aided by the establishment of a Registry. The Registry combines the observations of many individual investigators and physicians across the country and world.

Previous studies done with the Registry information were usually collaborative in nature with the Registry serving as a mechanism to identify physicians caring for patients with a particular disease – and the investigator then contacting those physicians to establish a research collaboration.

The original 8 Registries contain data on 2,060 patients distributed as shown below:

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic granulomatous disease</td>
<td>394</td>
</tr>
<tr>
<td>Common variable immunodeficiency disease</td>
<td>606</td>
</tr>
<tr>
<td>DiGeorge anomaly</td>
<td>325</td>
</tr>
<tr>
<td>Hyper IgM syndrome</td>
<td>118</td>
</tr>
<tr>
<td>Leukocyte adhesion defect</td>
<td>0</td>
</tr>
<tr>
<td>Severe combined immunodeficiency disease</td>
<td>147</td>
</tr>
<tr>
<td>Wiskott - Aldrich syndrome</td>
<td>186</td>
</tr>
<tr>
<td>X-linked agammaglobulinemia</td>
<td>284</td>
</tr>
</tbody>
</table>
1.3 **Risk/Benefits**

There are no known potential risks to the patients who wish to enroll in the patient Registry. Due to primary immunodeficiency diseases being rare, no one physician sees enough patients to be able to form a representative picture of these diseases. By allowing patient medical information to be combined with that of thousands of other patients, each participating patient will be helping to establish a valuable comprehensive database for researchers.

1.4 **Purpose**

The purpose of this study is to build a national registry of data from subjects with primary immune deficiency diseases, and in some cases, those subjects who are carriers of genes that lead to immune defects. The data collected will include demographic, immunologic and health data on a large group of patients to discover the frequency of certain complications (autoimmunity, cancer, hepatitis, etc.), the age of the subjects, relationship between immune function and outcomes, race/or ethnicity, and cause of death if known. The research study will provide data on a number of subjects with these rare immunodeficiency disorders to a national database; the goal is to discover basic outcome data, ethnic and racial characteristics, kinds of complications, etc., of these immune defects. The Registry will provide a minimum estimate of the prevalence of each disorder in the United States, a comprehensive clinical picture of each disorder, and it will provide a resource for clinical and laboratory research.

1.5 **Trial Conduct**

This study will be conducted in compliance with:

- The National Health and Medical Research Council’s National Statement on Ethical Conduct in Human Research (2007).
- The protocol approved by the Institutional Review Board and according to Good Clinical Practice standards. No deviation from the protocol will be implemented without the prior review and approval of the IRB except where it may be necessary to eliminate an immediate hazard to a research subject. In such case, the deviation will be reported to the IRB as soon as possible.

This is a longitudinal study and will have multiple sites conducting the trial. All sites that are required to obtain approval from their IRB must do so prior to initiating the start up of the trial. If a site does not have an IRB, the site may request to operate under the main site’s (USIDNET Towson, MD) FWA number.

1.6 **Population**

The Registry will collect data to represent all patient populations with primary immune deficiency diseases. USIDNET will also, as appropriate, collect data on carriers of immune defects as these may reveal additional important immunologic or clinical data.
The goal is to discover basic outcome data, ethnic and racial characteristics, kinds of complications, etc; of these immune defects.

1.7 Literature

- Hyper IgM Syndrome - See Winkelstein, Marino, Ochs et al., " The X-linked Hyper-IgM Syndrome: Clinical and Immunologic Features of 79 Patients", Medicine, Vol. 82, No. 6, Nov. 2003, p.373-83.

2.0 Trial Objectives

The patient Registry is designed to obtain longitudinal data on a large number of patients with primary immunodeficiency diseases, and in some cases, genetic carriers of these defects in order to:

- Learn more about the phenotypic variations seen in a large number of individual patients with the same molecular diagnosis.
- Determine the natural history of these genetic disorders of immunity and establish genotype-phenotype correlations.
- Learn effects of various treatment protocols used in these patients over the course of time including unexpected side effects that may be unique to a particular diagnostic group.
- To evaluate measures of quality of life in patients with these disorders and correlate these with genotype and treatment history.
- To promote collaborative research amongst interested investigators by identifying a larger pool of potential research subjects than would be available to these investigators at their own institutions.
- To identify patients with a specific diagnosis for potential participation in multi-institutional clinical trials designed for diagnosis or therapy of their specific disease.

3.0 Trial Design

The design of this Registry involves a “Core” set of data that will be collected on all patients being enrolled in the Registry irrespective of their diagnosis (Appendix 1.0). When the patient’s specific diagnosis is recorded, a subsequent Disease Specific Data Entry Form will be seamlessly joined to the Core Form during the web data entry session. Included in these forms are sections for diagnostic criteria and grade, and a description of the clinical spectrum of the disease seen in patients with that diagnosis. These Disease Specific Data Forms are designed to collect data that is more specific for the particular diagnosis of the patient and includes things such as laboratory diagnostic tests that are important for that disease, genetic mutation analysis for the gene(s) involved with that diagnosis, and treatment related items that are more specific to that diagnosis.
Experience with the previous Registry suggested several keys to help participation:
- The interests of the participating academic investigators must be protected if they are going to be willing to register their patients and provide useful data -- they need to get something positive in return for their efforts.
- Keep the data entry process as user friendly as possible.
- Provide suggested responses (using pull-down menus is one way to achieve this level of being user-friendly).
- Ask enough specific questions to permit the “rule-out” of a misdiagnosis.
- Provision of data entry assistance to centers that follow a larger number of patients will help encourage their participation.

For access to the data contained in the Registry, an interested investigator must submit a request outlining the experimental question being asked and the specific data requested. This request will then be reviewed by a designated USIDNET staff member, the Steering Committee and where appropriate, the disease specific working group. Upon approval, and if the data is available in the Registry, a report will be generated by the database technical manager to answer the query. If the request involves data that is not found in the database in sufficient detail, the Steering Committee may allow the requesting investigator to have a list of physicians who have submitted patients matching the search criteria. The investigator would then be responsible for contacting those physicians and establishing a research collaboration to complete acquisition of the data needed for the study.

Only this formal request process will allow access to the Registry data and only the data requested will be provided. Browsing through the database will not be permitted. However a submitting physician will have access to all of the data that he/she submitted on a patient and will be able to provide periodic updates.

A subject may select one of three ways to join the Registry:

**OPTION ONE**, the subject’s identity will not be stored in the Registry. The subject’s name, date of birth and mailing and/or email address will be used by the investigator at the site but will not be entered in the Registry or given to the study sponsor. A code number will be assigned to his/her information in the Registry, but only the investigator at the site will know it. The Registry Steering Committee may direct the Registry staff to send reports containing information about the subject’s disease to the investigator. The Registry committee may also permit information about proposals to study new tests or treatments to be sent to the investigator. The subject will not be contacted directly by the Registry staff because the subject will be de-identified.

**OPTION TWO**, the subject’s name, full date of birth and mailing and/or email address will be recorded by the Registry Staff and kept in a database that is separate from any information about the subject’s condition. The subject’s specific medical information will be assigned a code number when it is included in the Registry. The only link between the subject’s name and the medical information in the Registry will be the code number. The investigator and study staff may periodically update the subject’s information to include
changes in his/her condition or treatment as well as changes in his/her name or contact information. Investigators reviewing the subject’s medical information contained in the Registry database will not have access to a subjects’ identifying information.

Under **OPTION TWO-A**, communication between the Registry and the subject will be carried out by the investigator. The Registry staff will send all information to the investigator and he/she will then transmit that information to the subject. This may include new information about their disease, new treatments, or future research opportunities. The only circumstance where the Registry staff might contact the subject directly would be in the case that the subject has moved and/or ended contact with the original investigator or the original investigator has retired or for some other reason can no longer be contacted by the Registry staff.

Under **OPTION TWO-B**, the Registry staff may get in touch with the subject directly to inform him/her about research results based on information gathered about the subject’s disease. Registry staff may also ask the subject to clarify items that might be confusing about information in the Registry or they might ask if the subject wishes to update or add to his/her information in the Registry. The Registry staff may also send the subject notices about new research studies being planned that he/she may be eligible to join if the subject wishes. The investigator would also receive these notices at the same time as the subject so that they may discuss the new studies together.

### 3.1 USIDNET’s Collaboration with the Center for International Blood and Marrow Transplant Research (CIBMTR)

USIDNET is currently working with the Center for International Blood and Bone Marrow Transplant Research (CIBMTR) in the collection of data from individuals with primary immune deficiency diseases who are treated by bone marrow or stem cell transplantation. All bone marrow and stem cell transplants in the United States, must by law now be reported to a central database held by the CIBMTR, which is, like the USIDNET Registry, a password-protected database with assigned code numbers rather than patient names. The data collected before and after transplantation in the USIDNET Registry are important for those doctors who perform the bone marrow/stem transplantation. The data will be used for approved research projects to determine best practices for transplants. During and after the stem cell transplantation, doctors will collect and submit clinical data, laboratory details and the status of the transplant to the CIBMTR Registry. During this process, parents/patients will be informed about the data being collected in the CIBMTR Registry. The goal of the USIDNET Registry and the CIBMTR and its research partners, is to share the collected data so that each data set can be complete. USIDNET and CIBMTR have worked together to harmonize the data forms so that patient data does not have to be completely re-entered if a transplant is performed. The assigned coded numbers will be used for all data sharing.

### 3.2 Primary Study Endpoints/Secondary Endpoints

There are no primary or secondary endpoints for this study.
3.3 **Duration**
The authorization of a patient for use of their Personal Health Information (PHI) for this specific study has no expiration date.

3.4 **Discontinuation**
Although an authorization for research uses and disclosures need not expire, a research subject has the right to revoke, in writing, authorization at any time. The individual's revocation is effective when the covered entity receives the written revocation, except to the extent that the covered entity has taken action in reliance upon the authorization. For example, a covered entity is not required to retrieve information that it disclosed under a valid authorization before receiving the revocation. For research uses and disclosures, the reliance exception would permit the continued use and disclosure of PHI already obtained pursuant to the authorization to the extent necessary to protect the integrity of the research, for example, to account for a subject's withdrawal from the research study, to conduct investigations of scientific misconduct, or to report adverse events.

3.5 **Data Identification**
Data will be supplied to the USIDNET on paper forms. The USIDNET staff or a designated data entry person will enter data into the computer database. Repository data management will be the responsibility of the USIDNET staff or a designated data entry person. After the database is queried and data exported, further data management will be performed by investigators using the database or the Registry data management team. The identity of individuals who are part of the Registry will not be made public in publications based on Registry information. The identity of individuals providing information obtained will be kept confidential to the extent permitted by law. If required by law or regulation, your identity may be revealed to government agencies, such as the U.S. Office for Human Research Protections (OHRP) or the Department of Health and Human Services (DHHS), individuals who are involved in the study (or authorized to monitor or audit the study), or the IRB.

4.0 **Selection and Withdrawal of Subjects**

4.1 **Inclusion Criteria**
1. Must have a primary immune deficiency disease or be a genetic carrier of such a defect.
2. Subject must give Informed Consent or Assent.

   **Consent and Assent Instructions:**
   - **Consent:** Subjects 18 years and older must sign on the subject line
   - For subjects under 18, consent is provided by the Legally Authorized Representative
   - **Assent:** Is not required for subjects 12 years and younger
   - Is required for subjects ages 13 through 17 years

3. All individuals of all ages and genders with an immunodeficiency disorder will be accepted for registration providing that there is evidence consistent with the diagnosis of a primary immunodeficiency disorder.
4. The initial Registry was established with 8 disease specific sub-Registries, but the intention is to broaden the number and scope of sub-Registries to include as many of the recognized primary immunodeficiency disorders as possible. We are also developing a data entry format that will permit registration of individuals that meet the usual criteria for a defect in immunity but who do not fit into one of the previously described immunodeficiency disease groups or are a genetic carrier of such a defect.

4.2 Exclusion Criteria
1. Individuals with immunodeficiency associated with HIV infection, chemotherapy or other immunosuppressive therapies will not be accepted for registration unless there is clear evidence that these individuals also have a genetically determined immunodeficiency disease as well.
2. Individuals who do not give informed consent will also be excluded.

4.3 Subject Withdrawal
A patient may withdraw authorization of his or her permission for the use and disclosure of their personal information for research, but he or she must do so in writing to the Principal Investigator (PI) at the address stated above. If the patient withdraws permission, the PI for the study may still use or share that information that was already collected if the information is necessary to complete the study.

4.4 Enrollment/Recruitment Methods
Subjects will mainly be recruited in person in outpatient and inpatient clinical areas or other satellite facilities. Subjects will also be recruited via telephone after mailing consent forms with cover letters to their homes. The USIDNET will make every attempt to avoid repeated invitations to participate to patients who are already informed regarding the study and have declined to participate either in person or by telephone. Other methods of recruitment are: direct subject contact via www.primaryimmune.org, referrals from physicians, the IDF National Conference and other various conferences held.

5.0 Assessment of Safety

5.1 Adverse Event Reporting
All adverse events should be reported to the USIDNET. The reports should be followed promptly by detailed, written reports. The immediate and follow-up reports should identify subjects by unique code numbers assigned to the trial subjects.

The investigator should also comply with applicable regulatory requirements related to the reporting of unexpected serious adverse events to the IRB.
Breach of confidentiality constitutes an adverse event for this protocol. If a patient does not consent to inclusion of identifying information in the protected demographic subsection of the Registry and we discover that such information was submitted, the IRB and the subject will be informed of the event. The information will be removed from the demographic section of the Registry. If the patient does consent to the inclusion of identifying information and we learn that information is released to an outside investigator (contrary to the policy of the Registry’s operation), we will inform the IRB, the subject, and USIDNET of the breach of confidentiality. In either case, we will ask the subject whether or not they wish to continue to participate in the Registry or (if applicable) if they wish to continue to have their protected information included.

5.2 Definitions

1. **Adverse Event** - an unanticipated problem involving “risk” to subjects that ultimately results in breach of confidentiality. AE reports must be filed with the sponsor and the Institutional Review Board (IRB) when any of the following happens to a subject on a study.

5.3 **Adverse Event Follow-up**

Occurrence of any Adverse Event will be communicated to USIDNET within 24 hours of the investigator’s discovery. The communication can be by phone and/or fax. The IRB on record will also be notified within 24 hours of the occurrence.

All follow-up information will be forwarded to USIDNET within five working days of receipt.

The Principal Investigator or designee will be responsible for obtaining and reviewing records if possible.

All Adverse Events must be followed by the Investigator or designee until the AE has been resolved.

6.0 **Statistical Methods**

6.1 **Data Management and Statistical Analysis**

a. **Data Management Methods** - Data will be supplied to the USIDNET on paper forms. The USIDNET staff will enter data into the computer database. Repository data management will be the responsibility of the USIDNET staff. After the database is queried and data exported, further data management will be performed by investigators using the database.

b. **Quality Control Method** - Data will be verified by investigators after being loaded into the database.
c. **Data Analysis Plan** - The analysis plan will depend on details of each investigator’s query. The plan will be subject to review by each disease or DSWG committee during the process of applying to query the database.

d. **Statistical Power and Sample Considerations** - These will depend on details of each investigator’s query.

e. **Study Organization** - The USIDNET Steering Committee is responsible for management of the database. There are disease-specific subcommittees that assist with procedural and technical matters as they relate to particular disease subcategories of entries in the database. Mainly, these include determining what data is to be collected and assisting in the process of approving database queries by investigators, when necessary.

f. **Data and Safety Monitoring Plan** - The USIDNET Registry Committee together with the USIDNET administrative staff will monitor all operations of the database. All data that is to be released to investigators will be reviewed prior to release to ensure maintenance of confidentiality.

6.2  **Deviation Reporting**

The principal investigator and the project director are responsible for reporting all major protocol deviations occurring at the site to the IRB.

1. All deviations will be reported as soon as possible, but no later than 5 working days after the investigator becomes aware of the event.

2. The investigator will complete, sign and submit a protocol deviation report. On the deviation report, the site must include the facts of the case, including: subject identifier, the date of deviation, impact on the subject’s confidentiality, and plan for preventing the deviation in the future.

3. If the IRB requires additional information, a letter will be sent to the investigator requesting additional information.

4. The IRB will determine if additional actions or follow-up are required. The USIDNET will permit direct access to source data/documentation.

5. It trial-related monitoring, audits, IRB/IEC(s) review and regulatory inspection(s) to review the patient data by providing direct access to source data/documentation.

6. Direct Access to Registry Data/Documentation - Identifiers will be stripped at the USIDNET before storing the data in the Registry.

7.0  **Quality Control and Quality Assurance**

Data will be verified by investigators after being loaded into the database. Trained Registry management personnel as well as the USIDNET Disease Specific Working Groups will also perform Quality control checks on the data to ensure accuracy and reliability.
8.0 Ethical Considerations

This study will be conducted according to U.S. and International Standards of Good Clinical Practice (FDA regulations 21 CFR 312 for IND studies and FDA guidance E6) for all studies. Applicable government regulations and procedures will also be followed.

This protocol and any amendments will be submitted to the reviewing Institutional Review Board for formal approval to conduct the study. The decision of the IRB concerning the conduct of the study will be made in writing to the investigator. All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. This consent form will be submitted with the protocol for review and approval by the IRB. The formal consent of a subject, using the IRB-approved consent form, will be obtained before that subject is submitted to any study procedure. This consent form must be signed by the subject or legally acceptable surrogate, and the investigator-designated research professional obtaining the consent.

9.0 Data Handling and Record Keeping

For the main Registry, a secure computer at the USIDNET office in Maryland will store all data with no personal identifiers. At the USIDNET office, the electronic Registry data and filing cabinets are restricted to separate, high capacity disks, i.e. Jaz and Zip, which are accessed from their own drives on the computer. Those drives, in turn, are accessed from a separate system configuration that has been established to further enhance security. The operator uses a distinct system configuration, one that only recognizes the high capacity disk drives, when he/she is using the database. The hard drive is not “seen” or opened on the computer during this time. In practical terms, this means, the operator cannot accidentally access the Internet while working with the data. As well as, in the event that the computer is stolen, the data will not be found on the computer. The Internet connection is on the computer’s hard drive. The operator uses another system configuration, one that only recognizes the hard drive, when he/she is using the Internet. A firewall program, Black Ice Defender, is used to prevent outsider intrusion into the computer itself during an Internet connection. An anti-virus program, Norton Antivirus, prevents viruses from infecting the computer and is updated every time new definitions become available. Both products are upgraded when new versions are offered.

To further enhance security, the high capacity disk is backed up at least daily, and stored in a secure location, so that there are always two copies of the electronic records. One copy is kept on site and one off site. This also addresses the concern for avoiding damage due to catastrophes, such as fire. Use of the electronic data base and filing cabinet is limited, and is password restricted. Archiving is also done at times, and paper records are filed in locked cabinets. The computer itself is kept in a locked facility to further prevent intrusion into the program or theft of the hardware.
10.0  **Finance and Insurance**

The USIDNET Consortium is supported by a five-year grant from the National Institute of Allergy and Infectious Diseases (NIAID) and the National Institutes of Health (NIH). This grant which was re-awarded in April of 2011 provides the infrastructure to run the USIDNET Registries. USIDNET also receives support from pharmaceutical/industry which helps fund different programs such as, but not limited to, Education and Mentoring Program, Registry Enrollment, Data Import and Updates, Chart Abstraction, Travel, programming upgrades and IRB Annual Reviews.

Appendix 1.0 CORE FORM
<table>
<thead>
<tr>
<th>Column 1</th>
<th>Column 2</th>
<th>Column 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Data 1</td>
<td>Data 2</td>
<td>Data 3</td>
</tr>
<tr>
<td>Data 4</td>
<td>Data 5</td>
<td>Data 6</td>
</tr>
</tbody>
</table>

**Legend:**
- [X] Indicates presence
- [-] Indicates absence

**Table Notes:**
- Column 1: Description or category
- Column 2: Specific details or values
- Column 3: Additional notes or details