

**Part B: Experimental Design and Protocol – ALL APPLICANTS MUST COMPLETE THIS FORM**

All investigators must submit a completed Part B with their New Protocol or 3 Year Rewrite application. If a protocol from a corporate sponsor or cooperative group is available, this must also be submitted.

Each question in Part B should be answered thoroughly with answers that are specific to how the research will be conducted at Children's Hospital, Boston.

Do not cut and paste from the protocol or from a grant application to complete Part B. Instead, complete each question in Part B by referencing the applicable page and section number of the protocol which answers the questions in Part B. For some questions in Part B, such as those regarding recruitment methods, confidentiality provisions, and adverse event reporting, you will need to provide complete answers rather than references to the protocol, since the protocol will not address these items as they apply specifically to how the research will be conducted at CHB.

Further information may be obtained by referring to [the policies and procedures on the CCI website](#)

**Please provide a brief summary or abstract of this research protocol.**

The United States Immunodeficiency Network (USIDNET) is a NIH-funded consortium of researchers of primary immunodeficiency diseases (PIDD). The consortium has established 6 Committees to organize, manage, and accomplish the overall aims and goals of the consortium. The Committees are: Senior Advisory, Advisory, Steering, Education/Mentoring, Repository, and Registry. This protocol is for the establishment of Children's Hospital Boston as a participating center for the collection and submission of clinical and demographic data on our PIDD patients to the USIDNET Registry.

**1. Specific Aims /Objectives**

This patient registry is designed to obtain longitudinal data on a large number of patients with the rare primary immunodeficiency diseases 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

**2. Background and Significance**

The primary immunodeficiency disorders are thought to be very rare, although their true prevalence has been difficult to estimate for several reasons. Although untrue, it is still taught in some medical schools that the primary immunodeficiency disorders are so rare that it is not worth the effort to learn about them since it is unlikely that the average physician will ever see such a case. It is true that real advances in the understanding of these disorders have been made by a limited number of institutions around the world that were able to accumulate sufficient patients to begin making sense of the range of symptoms that these patients exhibited.

With the completion of the human Genome Project an explosion of different immunodeficiency disorders defined by mutations in unique genes have been described now totaling 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 of patients with these disorders that would combine the observations of many individual investigators and physicians across the country and world.

**3. Preliminary Studies/Progress Report**

In 1992 the NIAID/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 Director of the Registry during the first 10 years of its operation was Dr. Jerry Winkelstein of the Department of Pediatrics at the Johns Hopkins University Medical Center in Baltimore. 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 IRB at Johns Hopkins served as the IRB for the Registry and issued a *waiver of consent* citing the design of the Registry that lacked specific name, address, social security numbers or other specific identifiers and that mandated any contact with the patient could be made only through the submitting physician - who presumably would still know the patient's identity. In practice this design somewhat limited the usefulness of the Registry for longitudinal data collection since it meant that if a physician left practice there was no way to update their data or reach the patient because their identity was known only to that physician. In addition, the amount of data collected in the original registry was quite limited and useful primarily to reassure the Registry that the patient's diagnosis was likely to be correct. 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 eight Registries contain data on 1424 patients distributed as shown below:

Chronic Granulomatous Disease	396
Common Variable Immunodeficiency Disease	362
DiGeorge Anomaly	56
Hyper IgM Syndrome	109
Leukocyte Adhesion Defect	0
Severe Combined Immunodeficiency Disease	129
Wiskott-Aldrich Syndrome	169
X-Linked Agammaglobulinemia	203

The contract for continuing operation of these registries was included when NIAID and 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. 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 beginning in October 2003. Dr. Hans Ochs of the University of Washington is the PI and Dr. Charlotte Cunningham-Rundles of Mt Sinai Medical Center in New York is Co-PI.

The Steering Committee of the USIDNET 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 that similarly contains 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. USIDNET is in the process of implementing a modified version of the ESID data entry system for the original eight disorders in the IDF Registry. It is not known when the on-line data entry system will be available. However, the NIAID has mandated that all data in the eight existing IDF Registries be ported into the new electronic database so that none of the original patient data is lost. Together, these databases should provide the research community with a very powerful new tools to facilitate study of these individually rare disorders.

#### **4. Design and Methods**

##### **a. Study Design**

Eight sub-registry committees have been established by USIDNET to cover each of the disease categories in the current registry and we anticipate adding additional committees as new disorders are added to the Registry. The duties of the committees are:

- To act as an advisory body to review and approve requests to access the data contained in the database for that sub-registry.
- To design and periodically re-evaluate the data collection forms being used for their specific sub-Registry and to keep the data collection up-to-date to reflect advances in science and clinical practice.
- To develop research protocols that can be addressed using the Registry data or patient/physician list and to recruit colleagues to submit patients for the Registry.
- To act as a publication committee to prepare periodic reports or to recruit authors to prepare reports on the data being collected on specific disorders covered in their Registry.

The current model calls for all of the data accessible to researchers submitting queries to the Registry to be de-identified, although the patients will be given the option for the Registry to retain identifying data in a separate secure file linked by a unique assigned number. This Registry, as was the earlier IDF Registry, is intended to be a physician Registry with primary interactions between the Registry and the patient being carried out through the Submitting Physician. The intent is also for subjects to have the choice as to whether or not any protected health information (PHI) is submitted to the registry. If patients choose to withhold PHI, the registry would contain only a coded entry with gender and age. If they chose to include PHI, it would be held in a distinct segment of the database. Only those individuals who maintain and operate the registry would have access to the PHI segment. Investigators who provide data to the registry would have access to the PHI for patients from their own institution only. Investigators who submit research queries to the database would never have access to any PHI.

The Steering Committee of USIDNET has recommended that all submitting physicians who wish will be acknowledged or offered co-authorship in any publications using data from a patient that they have submitted. In addition, USIDNET is training staff that will be able to travel to various medical centers and physician's offices to assist in the entry of patient data.

The design of this new Registry involves a "Core" set of data that will be collected on all patients being enrolled in the Registry irrespective of their diagnosis. When the patient's specific diagnosis is recorded a subsequent "disease specific data entry form" will be joined to the "core" data form. 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 or genes involved with that diagnosis and treatment related items that are more specific to that diagnosis.

Our experience with the previous IDF 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
- Keep the data entry process as user friendly as possible
- 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

The existing plan for access to the clinical data contained in the Registry involves several steps. An investigator must submit a detailed written request outlining the experimental question being asked and the specific data required. This request will then be reviewed by the Registry Director and by the disease sub-registry oversight committees involved, if necessary. Upon approval, if all the requested data is contained in the Registry database - a formal 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 requesting investigator will be provided a list of physicians who have submitted patients matching the search criteria of the request and the investigator will then be responsible for contacting those physicians and establishing a research collaboration to complete acquisition of the data needed for the study. At no time will researchers querying the database have access to any patient identifying information.

Only this formal request process will allow access to the registry data and then only the data requested will be provided. Browsing of the database will not be permitted. However, a submitting physician will have access to all of the data that he/she submitted on patients and will be able to provide periodic updates. Such updates will become an important part of the Registry permitting longitudinal follow-up to evaluate the effectiveness of various treatments, etc.

The USIDNET Steering Committee has decided that qualified investigators from academia and industry will be allowed access to the Registry via this query mechanism. In addition, certain limited queries from the lay public may also be accepted. The committee has further recommended that reports containing the results of all queries will be posted on the USIDNET website to allow broad distribution of the information generated. However academic investigators will be permitted to embargo release of that data for up to 15 months to permit time for a scientific report to be prepared and published. Investigators from industry will not be allowed such an embargo period so as to not give unfair commercial advantage to one company over another.

**b. Patient Selection and Inclusion/Exclusion Criteria**

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. The initial Registry is being established with eight 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 diseases.

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.

Individuals who do not give informed consent will also be excluded.

**c. Recruitment Methods**

i. HOW, WHERE and WHEN will potential subjects be recruited?

Subjects will mainly be recruited in person in outpatient and inpatient clinical areas at Children's Hospital or satellite facilities. Subjects will also be recruited via telephone after mailing consent forms with cover letters to their homes. We 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.

ii. WHAT recruitment methods and materials (e.g. posters, fliers) will be used? - *attach all materials*

Recruitment will be in person or via mail/telephone. A notice will be handed to clinic patients asking them to discuss participation with their doctor.

iii. WHO will be responsible for subject recruitment?

Faculty, fellows, and clinical research staff of the Division of Immunology, Children's Hospital.

**d. Description of Study Treatments or Exposures/Predictors**

None.

**e. Definition of Primary and Secondary Outcomes/Endpoints**

None as such.

**f. Data Collection Methods, Assessments and Schedule** (what assessments performed, how often)

Medical record review, no subject participation is required beyond giving consent.

**g. Study Timeline (as applicable)**

N/A

**h. Adverse Event Criteria and Reporting Procedures**

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 CCI 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 CCI, 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.

- i. **If the Investigator is the Sponsor/Assignee (IND or IDE-holder), he/she is responsible for selecting a qualified monitor who will monitor the progress of all clinical investigations conducted under the IND or IDE. Please describe the monitoring plan for this protocol below:**

↳ Note: the EQuIP office provides monitoring services and advice. For info, contact EQuIP @ 5-7052.

Not applicable

## 5. Data Management and Statistical Analysis

### a. Data Management Methods

Data will be supplied to the IDF on paper forms. IDF staff will enter data into the computer database. Repository data management will be the responsibility of IDF 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 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 Registry 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. These include principally 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 IDF administrative staff 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. Risks and Discomforts

The only significant risk associated with this protocol is breach of confidentiality (see 4h). Patients may experience some emotional discomfort when being asked to participate.

## 7. Potential Benefits

There is not likely to be direct benefit to patients from participation. It is possible that study of the Registry data over time may lead to improved diagnosis, prognosis, and therapy for these disorders.

## 8. Privacy Provisions

Patient privacy will always be respected in any study activity. For this study, this is limited to the process of obtaining informed consent.

**9. Confidentiality Provisions**

At the USIDNET office, paper records are kept in locked cabinet with access restricted to USIDNET or IDF personnel. The electronic Registry data are restricted to separate, external drive disks which are accessed from a computer. Those drives, in turn, are accessed from a separate system configuration (partition) 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 computer's hard drive and associated applications are not "seen" or open on the computer during this time. In practical terms, this means that the operator cannot accidentally access the Internet while working with the data. It also means that 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 protected. The computer itself is kept in a locked facility.

**10. References**

**11. Appendix Materials** – please check off as appropriate if included with submission.

- Sponsor's Protocol
- Investigator brochure (3 copies)
- Flow charts, schemas
- Other:Registry data collection forms
- Materials given to subjects (reminders, letters, thank-you, etc.)\*
- Federal grant application (3 copies)
- Survey, questionnaires, assessments
- Recruitment letters, postings, flyers

\* see instructions for further information