A CASE CONTROL ETIOLOGIC STUDY OF SARCOIDOSIS
ACCESS

PROTOCOL

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CHAPTER 1

OVERVIEW OF OBJECTIVES AND DESIGN

1.1 INTRODUCTION

A Case Control Etiologic Study of Sarcoidosis (ACCESS) is a multicenter study sponsored by the National Heart, Lung and Blood Institute (NHLBI). The study is a case control study to investigate the etiology of sarcoidosis. The primary investigation is the study of etiology in which 720 patients with sarcoidosis representing both men and women, white and minority race/ethnicity and the spectrum of disease severity will be enrolled as will 720 age, gender and race/ethnicity matched controls recruited through random digit dialing to represent the general population. A prospective cohort study of the first 240 cases enrolled in the case control study will be used to define categories of outcome that may be related to the etiology of sarcoidosis and to describe the clinical course of sarcoidosis.

Sarcoidosis is a systemic granulomatous disease of unknown etiology. The organ systems most frequently of concern in sarcoidosis are the respiratory system (especially the lower respiratory tract, but also the large airways and upper respiratory tract), the eyes and the skin; involvement of the liver, nervous system, kidneys and the musculoskeletal system may be found. Sarcoid inflammation in vital organs (e.g., lungs, heart or nervous system) can be fatal, but for most patients the clinical course is benign.

Ten clinical centers, located at major medical centers/hospitals in the United States, are responsible for screening and recruitment of eligible sarcoidosis cases and matched controls. The ACCESS Clinical Coordinating Center is responsible for the study's statistical design, data collection and management, and analysis of study results. The Project Office, located in the Lung Biology and Disease Program of the Division of Lung Diseases at the NHLBI, is responsible for the overall direction and administration of ACCESS in collaboration with the Study Chairman, who was appointed by the NHLBI Director. A central repository for storage of case and control specimens is operated by McKesson Bioservices under a contract with the NHLBI. Specialized Core Laboratories also participate in the study.

1.2 OBJECTIVES

The case control study is designed to investigate possible causes and risk factors for sarcoidosis. Evaluation of cases and controls to determine the etiology of sarcoidosis will include an inquiry into environmental and occupational exposures, family history, medical history, and collection of blood specimens. Blood specimens will be used to identify potential immunogenetic and infectious contributions to sarcoidosis by means of specialized studies involving recently developed microbiology and nucleic acid analysis techniques such as HLA Class II marker studies, mycobacterial studies, immunogenetic studies, differential display polymerase chain reaction (PCR) studies, and comparisons of nucleic acid sequences from blood specimens to those of known pathogens. Bronchoalveolar lavage studies will also be performed. Specific hypotheses concerning the cause of sarcoidosis will address infections, genetic factors, and occupational or environmental factors as potential risk factors for sarcoidosis.

The clinical course study of 240 cases is designed to: (1) define sarcoidosis cases that do or do not clinically resolve over a two-year period of follow-up, and (2) develop a clinical / radiological / physiologic sarcoidosis assessment system for reporting the severity of disease.

1.3 STUDY RATIONALE

In spite of the advances in research on the cellular mechanisms of sarcoidosis, the underlying causes remain unknown. There may be some overlap between sarcoidosis and other granulomatous disease of unknown etiology (e.g., primary biliary cirrhosis and Crohn's disease), but these insights are of little help in determining the etiology of sarcoidosis (Spiteri et al, 1992). Recurrence of granulomatous lesions in sarcoidosis patients after lung transplantation also provides insight, but does not lead to clear conclusions as to specific etiologies (Bjørtuft et al, 1994; Johnson et al, 1993; Martinez et al, 1994).

Etiologies including infectious agents such as mycobacteria (Mitchell et al, 1992; Fidler et al, 1993), lifestyle habits such as pica (clay eating and starch eating) (Comstock et al, 1961), place of residence (rural versus other) and environmental exposures such as pine pollens and occupational

exposures (Comstock et al, 1961; Cummings et al, 1959; Douglas, 1961; Dunner and Williams, 1961; Gentry et al, 1955; Horwitz, 1961; Keller, 1971; Nobechi, 1969; Sartwell, 1983; Teirstein and Lesser, 1983) have been investigated in clinical studies of sarcoidosis. But no credible etiologic agent has been identified. Rural residence has been associated with sarcoidosis (Buck, 1961; Buck and McKusick, 1961; Buck and Sartwell, 1961; Gentry et al, 1955), but some investigators suspect this association is a result of confounding (Sartwell, 1983; Teirstein and Lesser, 1983). The most compelling observation has been an unquantitated but striking familial aggregation found in the classic case control studies of Buck, Sartwell and McKusick (Buck, 1961; Buck and McKusick, 1961; Buck and Sartwell, 1961). The main shortcomings in all of the case control studies, including those of Buck and colleagues, have been the small number of cases and controls (Buck studied 62 cases), and possible biases in selection of controls.

Sarcoidosis has been well characterized pathologically, and the most interesting research results in recent years have addressed the cellular mechanisms of disease activity. Conclusions about etiologic factors that would be of use in treatment or primary prevention of sarcoidosis have been difficult to reach. Previous studies of the etiology and natural history of sarcoidosis in the United States, especially in black patients in the United States, have been limited by relatively small numbers of patients. Recent advances in laboratory methods (e.g., polymerase chain reaction technology), control selection and statistical analysis methods (e.g., methods for random digit dialing and synthetic case control data analysis) will be of use to address the etiology of sarcoidosis. Promising leads to the etiology of sarcoidosis have come from diverse sources: in clinical laboratory investigations alveolitis has been found to precede granulomatous inflammation; in case control studies familial aggregation has been identified; and in case reports recurrence of granulomatous inflammation has been observed after lung transplantation. Thus, it is appropriate now to identify a large number of patients with sarcoidosis, establish disease stage using standardized criteria, select an appropriate control for each case, and use case control methods to search for exposures or genetic predispositions which could cause alveolitis, exposures or genetic predispositions that would aggregate in families, and exposures or genetic predispositions

that would result in recurrence of sarcoid granulomas in transplanted lungs. The answer is not likely to prove to be a single, known exposure. An interaction of exposures with a genetic predisposition would be of great interest.

1.4 DESIGN FEATURES

Only newly diagnosed cases of sarcoidosis with tissue confirmation of granuloma and a clinical course compatible with sarcoidosis, that is, a systemic granulomatosis of unknown etiology are eligible for the study. Newly diagnosed cases are of interest for accuracy and consistency of recall. A newly diagnosed case is defined as a patient who had tissue confirmation less than six months prior to entry into the study. Initially, cases are recruited at each participating Clinical Center, without regard to type of clinical disease (i.e., erythema nodosum or Löfgren's Syndrome; acute or chronic sarcoidosis, excluding patients with fibrotic lung disease; fibrotic lung disease; or extrapulmonary sarcoidosis). Clinical Coordinating Center staff review the distribution of enrolled cases periodically to ensure that appropriate proportions of cases in each of the defined categories of disease are enrolled.

Population-based controls are selected through random digit dialing. Controls are matched to cases on age (within five years), gender and self-designated race (black, white, other). Random digit dialing facilitates the selection of a control group that approximates a probability sample in the population.

Only individuals 18 years of age or older are eligible. Cases or controls cannot have active tuberculosis or be taking anti-tuberculosis therapy or have a history of chronic beryllium disease. Potential controls with a past history of sarcoidosis, granulomatous hepatitis, primary biliary cirrhosis, Bell's palsy, undiagnosed uveitis, Crohn's disease and erythema nodosum of unknown etiology are excluded from the study. Cases and controls must be competent to sign consent forms for study participation and must be willing to participate in all required study evaluations.

Both cases and controls complete an entry evaluation for the collection of required data and biological specimens for future evaluation. The entry evaluation includes collection of demographic

information (age, gender, race, residence, marital status, etc.), medical history, environmental, and occupational exposure history, questions about the individual's family (first degree relatives), standardized psychosocial data on health related quality of life, and medical care usage.

The first 240 ACCESS cases are asked to participate in a two-year clinical course study. A clinic visit is scheduled between 24 and 30 months after the patient's baseline evaluation. The follow-up evaluation includes a medical history, physical examination, chest X-ray, spirometry, routine biochemistry, complete blood count and differential, and additional tests as clinically indicated. Clinical Center staff also contact these ACCESS cases by telephone at 6, 12 and 18 months after entry.

1.5 STUDY SIZE CONSIDERATIONS

1.5.1 Case Control Study

The proposed sample size of 720 cases and 720 controls for the ACCESS etiology study is adequate to identify associations of exposure variables between cases and controls with odds ratios of two or greater even when the prevalence of the exposure is small (proportion of controls exposed is 0.05). The planned statistical power is important since the etiology of sarcoidosis could be multifactorial and include several low-prevalence exposure agents.

Etiological factors may be different in certain age-race-gender groups. The large number of cases and controls in the ACCESS etiology study will permit stratification of the ACCESS population into smaller groups while maintaining adequate power (at least 80%) to detect moderate effects (odds ratios on the order of 3 or greater) when the prevalence of the exposure in the control group is slightly higher (proportion of controls exposed is 0.10). The large number of cases and controls will also help in determining whether certain groups have different risk factors (tests for interaction).

In certain substudies, large effects have been hypothesized. Even with 180 case and control pairs and a proportion exposed of 0.1 in the control group, the power to detect an odds ratio of 2.0 will be at least 86% (see Chapter 12).

1.5.2 Clinical Course Study

The clinical course study is conducted on the first 240 cases enrolled into ACCESS; each Clinical Center is expected to contribute at least 20 cases. The total number of cases is sufficient to detect small changes in means (three-quarters of a standard deviation) among defined subgroups, and moderate changes (odds ratios of 3) in categorical outcomes.

1.6 ANALYSIS PLANS

Although the etiology study includes as possible etiological agents a wide range of environmental, infectious, genetic, and sociodemographic exposure variables, the analytical plans for all of these agents are similar. Except for certain genetics studies, a matched case control design is used to identify those exposures or variables that have different prevalences or quantitative levels between cases and controls. Once identified, multivariate models are used to determine if the list of possible etiological agents can be further reduced to those that provide unique contributions to the risk equation. It is expected that matched-pair logistic regression will be used for these determinations.

It is planned to determine if different defined subgroups of the ACCESS population have different profiles of progression or regression of the disease over the course of two years. Analytical techniques for the clinical course study will include analysis of variance, regression, life table analyses, and standard analyses for categorical variables.

1.7 STUDY SCHEDULE

The recruitment period for ACCESS is November 1, 1996 through June 30, 1999. Clinical follow-up is performed for the first 240 cases in the study. Preserved specimens are stored in an NHLBI repository for later studies. Between July 1999 and June 2000, the ACCESS investigators will prepare reports for publication and presentation.

1.8 CONCLUSIONS

The etiology of sarcoidosis is unknown and has been a challenge to clinical investigation for decades. ACCESS will use a variety of recently developed laboratory and statistical methods to investigate the cause(s) of sarcoidosis. These new methods, such as polymerase chain reaction evaluations of nucleic acids, are more sensitive to potential etiologic agents than the methods employed in earlier studies. The number of histologically documented cases in ACCESS will be larger than any single previous study; the larger number of cases and controls also enhances the likelihood of identifying the etiology of sarcoidosis. By studying a large number of carefully documented cases and controls with new, sensitive methods, the ACCESS investigators will assess the etiology of sarcoidosis with a thoroughness that earlier studies could not achieve and that should produce substantial leads for future research on treatment and prevention.

CHAPTER 2

BACKGROUND AND LITERATURE REVIEW

2.1 INTRODUCTION

Sarcoidosis is a chronic granulomatous disorder of unknown cause associated with activation of T-lymphocytes and macrophages -- most commonly in the lungs (90%) (Crystal et al, 1981; James, 1994; Thomas and Hunninghake, 1987). Eye and skin involvement are seen in approximately 25% of patients, and symptomatic involvement of other organs in less than 10%.

The etiology of sarcoidosis has been of concern since it was first described (Hutchinson, 1892). Because of the similarity of the inflammatory response of the two diseases, sarcoidosis was considered at one time to be an atypical manifestation of tuberculosis. By the 1950s, the diagnosis of sarcoidosis was specific enough that studies could be performed to determine the incidence and prognosis of the disease (Cooch, 1961; Keller, 1971; Sartwell and Edwards, 1974). Among the epidemiologic methods available to determine the etiology of sarcoidosis the most appropriate is the case control method (Bresnitz and Strom, 1983; Comstock et al, 1961; Parkes et al, 1987) but the results from these studies have not led to a consensus regarding either an environmental or genetic causative factor. Most previous case control studies of sarcoidosis involved fewer than 100 cases and 100 controls. A multicenter study capable of enrolling larger case and control populations seems appropriate.

The prevalence of sarcoidosis is about one per 10,000 in most Caucasian populations, but African Americans are thought to have a disease prevalence about 10 fold greater than Caucasians (Cooch, 1961; Sartwell and Edwards, 1974; Teirstein et al, 1976; Terris and Chaves, 1966; Zaki et al, 1971). The preponderance of sarcoidosis in individuals in the 20-40 year old age range supports an etiologic factor with a latency period shorter than other chronic diseases such as lung cancer (due to tobacco smoking) or coronary artery disease (due to hyperlipidemia).

2.2 GENETIC ASPECTS

There are several reports supporting the concept that genetic susceptibility may contribute to or modify sarcoidosis (Brennan et al, 1984; Hillerdal et al, 1984; Honeybourne, 1980; Keller, 1971; Yamamoto et al, 1992). Marked variation occurs in the incidence of this disease for different populations. Irish women and Scandinavians have the highest incidence of this disease (Brennan et al, 1984; Hall et al, 1969). In one 15-year study of a stable population in Sweden, the cumulative risk of developing sarcoidosis was 1.4% for women and 1% for men (Hillerdal et al, 1984). There is a high incidence among Irish immigrants in London (Brett, 1965) and among persons of Scandinavian descent in Minnesota (Henke et al, 1986). In the United States, the incidence of sarcoidosis is higher for African-Americans than for Caucasians (Keller, 1971; Terris and Chaves, 1966; Zaki et al, 1971).

The manifestations of sarcoidosis are more severe in African-Americans than in Caucasians (Young et al, 1970; Young et al, 1974). Erythema nodosum is less common in African-Americans than in Caucasians, while lupus pernio is more frequent in African-Americans than in Caucasians (Izumi, 1992; Siltzbach et al, 1974). The perception that African-Americans have more severe disease than Caucasians has been challenged with the argument that the asymptomatic African-Americans are not likely to be identified in the United States health care system. However, West Indians appear to have more advanced disease than Irish or British when all three groups attend the same clinic (Honeybourne, 1980; Neville et al, 1983).

Familial sarcoidosis has been documented (Brennan et al, 1984; Hall et al, 1969; Harrington et al, 1994). Familial sarcoid has been reported to occur among 19% of African-Americans compared with only 6% of Caucasians in one American sarcoidosis clinic (Harrington et al, 1994). Genetic predisposition may underlie ethnic association. Monozygotic twins are more likely to have sarcoidosis in common than dizygotic twins (Wiman, 1972). There is also a report of a family with sarcoidosis in which the mother and two siblings were affected with sarcoidosis (Andrews et al, 1988). The two siblings had the same human leukocyte antigen (HLA) pattern.

Other studies of HLA haplotypes have been performed for population groups with inconsistent results. Some HLA types, such as B8, have been associated with sarcoidosis and a good prognosis (Guyatt et al, 1982; Hedfors and Lindstrom, 1983; Smith et al, 1981). Some HLA patterns are associated with a good prognosis in Japanese but a poor prognosis in Italians (Ina et al, 1989; Kunikane et al, 1987; Pasturenzi et al, 1993). A recent study comparing two different European populations with sarcoidosis summarized the associations of manifestations of sarcoidosis with HLA pattern and provided a predictive model for phenotypic expression of the disease based on the HLA type (Martinetti et al, 1995).

In the United States, HLA studies have been less complete (Raphael et al, 1993). There are reported differences in the HLA pattern of African-Americans with sarcoidosis compared to the general population (Eisenberg et al, 1978; Whitsett et al, 1983), but these results are difficult to interpret because of the poor characterization of HLA patterns in African-Americans.

HLA genetic molecules are known to play a direct role in the immune response in addition to marking genetic characteristics. Over the last 20 years, studies of the local immune response in sarcoidosis suggest that the granulomatous response is due to a prolonged stimulation of CD4+ T cells (Daniele et al, 1980; Hunninghake and Crystal, 1981). These cells are increased at the sites of disease and appear to be activated. Three possible mechanisms exist for the stimulation of CD4+ T cells: non-specific mitogenic stimulation; superantigenic mechanisms of polyclonal stimulation; and stimulation of CD4+ T cells through their antigen binding receptors with oligoclonal T cell proliferation -- the most likely mechanism according to recent observations (Dohi et al, 1994; Forrester et al, 1994; Grunewald et al, 1994; Tamura et al, 1990).

CD4+ T cells respond to antigen in the context of HLA Class II molecules. Class II molecules appear to be responsible for presenting foreign extracellular peptides to T cells (Neefjas and Momberg, 1993). Foreign (i.e., extracellular) protein is ingested by the antigen presenting cells (macrophages, dendritic cells, or B-cells). This foreign protein is partially digested in acidic endosomal compartments, and peptides produced by this digestion become bound to HLA Class II molecules. These peptides are 10-20 amino acids in length, and only a few critical amino acids

determine binding to specific HLA Class II proteins. The peptide bound to HLA Class II molecules is then transported to the cell surface where it can be available to bind specific T-cell receptors and result in the stimulation of the T cell. Peptides appear to bind to HLA Class II molecules competitively. Thus, if free peptide is available on the outside of the cell, this peptide could displace other peptides in the Class II groove and become bound to the Class II molecules. In addition, haptens, by binding to peptides, may also be presented to T cells as foreign substances.

Humans have three groups of Class II molecules that can present peptides to CD4+ T cells. These are HLA-DR, -DP, and -DQ. Since there are only a limited number of HLA Class II molecules (<200) that are available to bind the universe of foreign peptides, HLA Class II molecules bind peptides in a relatively non-specific manner. Only a few of the peptides in the hypervariable regions of the HLA Class II molecules appear to direct specific peptide binding (Marshall et al, 1994). Similarly, only 2 or 3 amino acids of the total peptide chain appear to be responsible for specific binding to HLA Class II molecules (Rammensee et al, 1993; Sinigaglia, 1994). Thus, the process of peptide binding to Class II molecules appears to require that specific motifs or sequences on the HLA Class II molecules determine the universe of peptides that can bind.

To determine if a specific set of peptides are active in a given disease, HLA Class II sequences must be determined. Serological Class II typing which has been used extensively in the past does not give this type of information. The importance of understanding molecular sequences can be seen in the human disease that is most similar to sarcoidosis, chronic beryllium disease. This condition appears to be identical to sarcoidosis except that it is known that beryllium, presumably acting as a hapten, can stimulate CD4+ T cells. Others have found (Richeldi et al, 1993) and it has been confirmed (Stubbs et al, 1994) that there is an association of glutamate at position 69 of HLA-DPB1 with beryllium hypersensitivity. Recent evidence suggests that positions 57 and 86 on HLA-DRB1 may also be important. Of particular importance is the observation that monoclonal antibodies specific for HLA-DR (L243) block the beryllium induced proliferative response. This observation supports the notion that HLA-DR is presenting the beryllium-peptide to the T-cell

receptor. HLA Class II molecular predisposition sets the circumstances for stimulation of a T-cell response that promote granuloma formation. HLA Class II type is genetically determined.

While HLA Class II typing most likely will identify a genetic predisposition to sarcoidosis, because of this molecule's important role in presenting antigenic peptides to CD4+ T cells, identification of HLA Class II sequences that are associated either with an increased incidence of sarcoidosis or a reduced incidence may be an important clue to the environmental agent(s) that cause sarcoidosis. This is known as "Reverse Immunogenetics" (Davenport and Hill, 1966). Previously the sequence of determining pathophysiology and preventive measures for specific infectious diseases has been as follows: first, a disease is identified; second, an environmental of infectious agent is identified; third, the critical antigens that are associated with the infectious agent are identified and shown to stimulate T cells; fourth, the specific peptides from the antigen are determined; and finally a vaccine that may be protective is produced. The approach taken with "Reverse Immunogenetics," however, begins with an identification of HLA associations with a disease; second, the peptides that preferentially bind to these HLA markers can be determined; third, the peptides can be tested against T cells to determine their reactivity; fourth, by searching protein databases, antigens that contain the reactive peptides can be found; and finally vaccines can be tested using these antigens. The process of "Reverse Immunogenetics" has been recently used to develop new vaccines for malaria (Hill et al, 1991). By a similar process, if consensus sequences can be determined for sarcoidosis, candidate peptides and antigens may be found for testing against bronchoalveolar lavage T cells. Thus, the identification of HLA Class II genes that are associated with sarcoidosis is a link to the etiologic agent of the disease. ACCESS Investigators intend to develop the first link in this process by determining HLA Class II associations with sarcoidosis as indicated in the goals and objectives (see Chapter 3).

Sarcoidosis may be a disease in which there is an interplay between multiple genetic and environmental factors. Elucidating these factors may be difficult because of the etiologic heterogeneity. The disease may aggregate but does not segregate in families. Thus, the genetic abnormalities in sarcoidosis may be predisposing but not predetermining. For diseases such as

sarcoidosis, if a specific gene is found to have a large role in the disease, and thus might be of etiologic importance, it may only account for a small proportion of the attributable risk.

Two basic approaches are available for identifying genetic causes of disease. One begins with documentation of familial aggregation, followed by segregation analysis, linkage analysis, and finally ends with molecular cloning of the gene. The other approach tests candidate genes. In case control studies, associations between genetic and environmental factors can be observed in cases compared to controls, and interactions between genetic and environmental factors can be tested. Both approaches would appear to be important in elucidating the genetic predisposition to sarcoidosis. In the proposed case control study, we will be able to study candidate genes during the course of the study. In addition, we plan to store specimens from sarcoidosis cases and controls for future studies of any candidate genes, such as may be determined by familial aggregation studies.

2.3 INFECTIOUS AND ENVIRONMENTAL ASPECTS

When injected under the skin, Kveim-Siltzbach agent (James, 1994) purified from the spleens of sarcoidosis patients leads to granuloma formation in over 75% of other patients with sarcoidosis (Siltzbach, 1964). The precise component of the Kveim agent responsible for its biological activity is unknown, but appears to be a heat stable, cell wall-associated particle. Similar granulomatous reactions can be observed when bronchoalveolar lavage (BAL) fluid from patients with sarcoidosis is treated like a Kveim-Siltzbach preparation and injected into the same patient. Although it may not be as specific as the original Kveim-Siltzbach agent, it is still associated with less than 10% false positives (Holter et al, 1992). Attempts to purify the Kveim-Siltzbach agent -- including culture techniques, filtering, subjecting to separation with serum from sarcoidosis patients, and the development of hyperimmune serum -- have been unsuccessful to date. The Kveim-Siltzbach suspension may contain either a causative organism or a protein product of a causative organism.

When sarcoidosis was first recognized as a disease, it was suggested that mycobacterial infection was the cause. Using sensitive polymerase chain reaction (PCR) techniques, it may be

possible to increase detection, while still retaining specificity. It may be that an infectious agent is only detectable in acute sarcoidosis, but "A major obstacle to PCR studies is the limited availability of tissue specimens that have been optimally preserved and obtained from patients that have undergone thorough clinical evaluation. Few centers would have sufficient material to compare the frequency of positive results in tissues from different organs, in patients with recent and chronic disease or patients with different clinical presentations. The possibility of establishing an international consortium should be considered to centralize collation of samples and permit comparisons between different groups using the same materials" (Mangiapan and Hance, 1995).

Other infections known to cause granulomas apart from those involving mycobacterial species include herpes, histoplasmosis, phaeohyphomycosis, treponematosis, sporotrichosis, cryptococcosis, coccidioidomycosis, cat-scratch fever and schistosomiasis (Su et al, 1992). Also, Listeria monocytogenes can cause granulomas (Ehlers et al, 1994), as can the agent of Whipples disease (Cho et al, 1984; Southern et al, 1989; Spapen et al, 1989), Rhodococcus sp., and Corynbacterium sp. (Van Etta et al, 1983). Over the last few decades influenza virus, para-influenza virus and mycoplasma have also been suggested as possible etiologic agents for sarcoidosis. Epidemiologic considerations make histoplasmosis, which is a common cause of a sarcoidosis-like disease, and exposure to the metal beryllium, unlikely global causes of sarcoidosis. Because of the occurrence of sarcoidosis in many different locales around the world, any etiologic agent(s) must have a similar, wide distribution.

Structures resembling leptospiral or large mycobacteriophage organisms have been identified in BAL fluid from subjects with sarcoidosis (Williams and Davies, 1986) and from the center of the granulomas (Wang et al, 1981). Similar structures have also been identified in the newly recognized syndrome of familial granulomatous disease (Chadarevian et al, 1993). While these unusual bodies may be the products of an infectious agent, one study has identified them as damaged platelets (Williams and Davies, 1986), raising the intriguing possibility of an altered platelet, perhaps associated with an infectious agent, as being associated with the etiology of sarcoidosis.

Although granulomatous areas may contain the putative infectious agent, this is not the only site where an infectious agent may be present. The granulomas in sarcoidosis are diffusely present throughout the body, suggesting that the etiologic agent is distributed through the blood system, at least at some point in the course of the disease. Thus, it is unlikely that the granulomatous areas, themselves, are the only sites that ever contain the etiologic agent. Many infectious agents that appear clinically to be organ specific, can now be detected in blood specimens using molecular techniques (Chryssanthou et al, 1994; Goodman et al, 1995; Murakami et al, 1994; Nichols et al, 1991; Patel et al, 1995; Schluger et al, 1994;). Blood samples (both cells and serum) should be examined using PCR amplification for any infectious agent DNA that may be present. If there is a candidate infection (i.e., M. paratuberculosis), then the tissue DNA preparations can be probed using primers that are specific for M. paratuberculosis. It is possible that any blood borne pathogen will be present in the "early" stages of the disease, and it may be absent from later cases.

One new molecular biology method is potentially capable of not only discerning an infectious etiology, but also providing additional information about genetic, environmental, and immunologic contributions to sarcoidosis. This technique involves the differential display of reverse transcription (RT) PCR products, and is termed differential display PCR (DD-PCR). DD-PCR involves the use of arbitrary oligonucleotide primers to amplify most mRNAs found in the cell using reverse transcription PCR, with modifications to target cDNA coding regions (Amac et al, 1994; Brenner et al, 1994; Gullans et al, 1994; Kojima et al, 1994; Liang and Pardee, 1992; Liang et al, 1992; Randall et al, 1994). For the ACCESS study, the DD-PCR reaction will be performed using RNA from cases and controls, and the PCR products from each reaction will be compared on polyacrylamide sequencing gels.

The priority with DD-PCR is to detect bands that are consistently observed in one group (either the case or control), but are infrequent in the other group of paired samples. Using recent modifications, including the normalization of background noise, the unique bands that are present in cases but not controls will be presumed to represent candidate genes specific for sarcoidosis. Such candidate genes could be of host origin or could represent genetic materials from an

infectious agent that is causally related to development of sarcoidosis. To identify and characterize the genes, unique bands are eluted from the gel, reamplified, and cloned into plasmids. The clones are sequenced and subjected to computer analysis to identify the genes and determine whether, for example, there is a specific gene of viral or bacterial origin.

Although DD-PCR is a technique that has been developed only recently, it has been used successfully to identify genes differentially expressed in a variety of conditions applicable to human disease, including oncogenes, tumor suppressor genes, and transplantation associated genes, as well as metabolically or developmentally induced genes (Aiello et al, 1994; Brunet et al, 1991; Liang and Pardee, 1992; Liang et al, 1993; Nishio et al, 1994; Russell et al, 1994; Utans et al, 1994; Zimmermann and Schultz, 1994). In humans, there is precedent for this technique using both peripheral blood specimens and small tissue samples, such as those obtained by renal biopsy (Gullans et al, 1994). Recent improvements have allowed comparisons of gene expression from individuals representing eight different ethnic groups (Brenner et al, 1994). Reproducibility for this technique has been shown in experiments identifying novel tumor suppressor genes in murine breast cancer, where the bands were reproducible (> 95%) for a given pair of primers and mRNA samples (Liang and Pardee, 1992; Liang et al, 1992).

Given that sarcoidosis may be a multifactorial disease, there is an advantage in selecting an approach which screens for several types of etiologic agents simultaneously. Using DD-PCR with arbitrary primers, all types of non-infectious and infectious etiologies, including viral and fungal as well as mycobacterial, can be detected. Furthermore, since previous successful laboratory studies have shown that paired samples and good controls are essential for interpretating DD-PCR (Sunday, 1995), the case control method of study using differential display with humans samples is an ideal approach.

This proposed case control study provides a good opportunity to use blood samples and new molecular techniques in biology to examine the question of whether sarcoidosis is due to an infection. The characterization of the cases enables correlations of any infection that is found with disease stage and with environmental and genetic factors.

Epidemiologic studies do provide several clues regarding an infectious or environmental agent for sarcoidosis. Manifestations of the disease can be seasonal (Bardinas et al, 1989; Henke et al, 1986; James, 1961; Putkonen et al, 1966; Selroos, 1969). The incidence of sarcoidosis is higher in health care workers than in the general population. Clusters of cases also imply infectious or environmental etiologies. A well documented clustering occurred on the Isle of Man, an area of Great Britain with a cloistered population (Hills et al, 1987; Parkes et al, 1985; Parkes et al, 1987). The most impressive finding in that study was a higher likelihood of contact with an individual with sarcoidosis among cases (39.6%) compared to controls (1.1%).

The lungs and skin -- two common target organs for sarcoidosis -- are regularly in contact with environmental antigens. Occupational and environmental exposures include many potential antigens that can induce sensitization -- a cell-mediated immune response responsible for the development of granulomas (Boros, 1988; Semenzato et al, 1985). Occupational and environmental factors cause a variety of granulomatous diseases that resemble sarcoidosis, including: chronic beryllium disease due to inhalation and sensitization by beryllium oxide, and other metal-induced granulomatous lung diseases (aluminum, titanium, zirconium); hypersensitivity pneumonitis due to both organic and inorganic antigens; tuberculosis and atypical mycobacterial infection; and fungal infections.

There is a marked predilection for disease to develop in early adulthood (age specific clustering), with the disease notably rare in children and early teens (Gordis, 1973; Pattishall et al, 1986) and rare in the elderly beyond age 70 (Cooch, 1961). This observation might suggest that exposure to the etiologic agent(s), whether they are antigenic or infectious, may first occur about the time that individuals reach working age, raising speculation about the contribution of occupational exposures.

Although studies vary in their findings with regard to the male:female ratios of sarcoidosis, most suggest a slightly higher rate in women. In the only population-based incidence study of sarcoidosis in the United States (Henke et al, 1986), however, similar age-adjusted incidences were

found in the two genders (5.9/100,000 person/years for men and 6.3/100,000 person-years for women).

Numerous studies, some case control studies, others case series, have observed a predilection for sarcoidosis to become clinically apparent in cold months -- winter and early spring (Bardinas et al, 1989; Henke et al, 1986; James, 1994; Putkonen et al, 1966; Selroos, 1969). If the latency between exposure to the causative agent and development of sarcoidosis-related symptoms is on the order of a few weeks to a few months, as is the case in animal models (Boros, 1988), contact with the etiologic agent, whether the agent is infectious or antigenic, occurs when people spend more time in closed, confined spaces at work or at home during winter months.

The preponderance of published data suggests that sarcoidosis occurs more commonly in the southeastern and middle Atlantic United States compared to other parts of the country (Michael et al, 1950; Sartwell and Edwards, 1974). Geographic clusters occur in other parts of the world, such as Denmark and United Kingdom (Horwitz, 1961; Parkes et al, 1987). This geographic distribution has promoted much speculation and a large number of studies that examined factors in the weather and soil (Buck, 1961; Comstock et al, 1961; Gentry et al, 1955; Terris and Chaves, 1966), plants, pine pollen and proximity to forests (Buck, 1961; Cummings et al, 1959; Douglas, 1961; Horwitz, 1961), water supply (Terris and Chaves, 1966), use of firewood (Buck, 1961; Terris and Chaves, 1966), and exposure to farm animals and pets (Buck, 1961; Terris and Chaves, 1966). Past studies have noted high prevalences where there is more lumbering activity (Cummings et al, 1959; Dunner and Williams, 1961).

A number of studies have associated sarcoidosis with rural residence, birthplace, or time spent in rural regions of the United States (Buck, 1961; Cooch, 1961; Gentry et al, 1955; Gundelfinger and Britten, 1961; Sartwell and Edwards, 1974). One case control study demonstrated cases were more likely to have been born in rural areas than were controls (59.6% versus 38.7%) (Buck, 1961). Seventy-one percent of cases had lived some time in rural areas prior to diagnosis, compared to matched controls (38.7%). Cumulative time spent in rural residence was also greater in the sarcoidosis patients. Unfortunately this investigation had several limitations: the

study populations were relatively small (62 cases and controls); definition of cases was poorly described; and, a third of controls were taken from an outpatient venereal disease clinic in an urban medical center which may have biased the controls to be urban dwellers.

There are several studies suggesting exposure to granuloma-inducing antigens at work (occupational clustering) (Bresnitz and Strom, 1983; Dunner and Williams, 1961; Keller, 1971; Parkes et al, 1987) is associated with sarcoidosis. In a review of sarcoidosis patients seen in the Veterans Administration system, there was evidence to support clustering in communities which had lumbering or wood milling as the principal local industry (Cummings et al, 1959). Other studies suggested increased incidence in mechanics, post office workers (Dunner and Williams, 1961) and firefighters (Kern et al, 1993). In one case control study (Bresnitz et al, 1986), there were several occupations with increased risk; the highest risk group were health care workers, an observation noted by others (Parkes et al, 1985).

2.4 IMMUNE FACTORS

A major breakthrough in the understanding of sarcoidosis occurred with the application of the technique of bronchoalveolar lavage (BAL) (Crystal et al, 1981; Hunninghake and Crystal, 1981). Up until that time, sarcoidosis had been characterized as a disease of down regulated immunity, the hallmark being the anergy found in the disease (Daniele et al, 1980). Leukopenia and lymphopenia were often observed in the disease (Lower et al, 1988). With the introduction of BAL, it became clear that sarcoidosis was characterized by increased number and activation of T cells and other components of cell mediated immunity in the area of inflammation. These studies demonstrated that peripheral blood studies provided little insight into the inflammatory response of the disease and that BAL provided unique information about the inflammatory response of the lung during disease activity.

Spontaneous resolution of disease was associated with a normalization of the CD4+ T cell to CD8+ T cell ratio prior to a fall in the proportion of lymphocytes in the BAL (Ceuppens et al, 1984).

In patients treated with corticosteroids, clinical response was associated with a fall in the CD4+ T cell to CD8+ T cell ratio in the BAL samples (Baughman and Lower, 1990; Ceuppens et al, 1984).

2.5 CLINICAL COURSE

The natural course of sarcoidosis can be quite variable (James, 1994). Up to 80% of patients will have self-limiting disease with no long-term sequela. A percentage of patients will be left with fibrotic disease but no chronic active disease. A small percentage of patients will have chronic, longstanding disease. The percentage of patients who have chronic disease varies from population to population. It has also been well established that certain manifestations of the disease are more likely to be associated with prolonged, chronic disease (Neville et al, 1983). For example, patients with lupus pernio, the disfiguring facial lesions of sarcoidosis, are very likely to have chronic and, perhaps, lifetime disease. Those patients with erythema nodosum and hilar adenopathy, on the other hand, have a better than 90% chance of resolution of the disease within two years and no evidence of recurrence in their lifetime. The two-year outcomes can be helpful to define categories of disease which may be related to etiology.

It has been suggested that patients with different ethnic backgrounds will have different outcomes. In sarcoidosis clinics in the United States, the percentage of patients with chronic disease is over thirty percent (Baughman et al, 1987; Johns et al, 1974). These clinics are often composed of predominantly African-American inner city patients. It is not clear whether the high percentage of chronic disease results from a selection bias on the basis of the investigator's interest in sarcoidosis or from the condition's natural history. There has been one report of a clinic in London in which chronic disease was seen in different frequencies depending on the patient's underlying ethnicity, with chronic disease seen much more frequently in West Indians than in Irish descendants (Honeybourne, 1980).

There are several ways that socioeconomic status may influence outcome of the disease. These include access to medical care, attitudes towards therapy, and social support. One advantage of this multicenter study is that cases will have a wide variety of social and economic

backgrounds so that the influence of these characteristics on disease presentation and two-year outcome can be examined.

2.6 CONCLUSIONS

The proposed multicenter, case control study will provide information essential to the ultimate determination of the cause(s) of sarcoidosis. The additional prospective study of clinical course will help to establish a broader perspective of the outcome of sarcoidosis patients.

CHAPTER 3

OBJECTIVES AND RESEARCH QUESTIONS

3.1 INTRODUCTION

The goals of ACCESS are to collect and analyze data and biologic specimens to address the hypotheses that (1) sarcoidosis occurs in genetically susceptible individuals through (2) alterations in immune response and/or (3) following exposure to environmental, occupational and/or infectious agents and that (4) genetic, environmental and socioeconomic factors affect initial pattern of organ involvement and clinical course (disease severity) over two years. Specific hypotheses to be addressed in the case control study are that genetic factors, infectious, occupational or environmental factors and immune alterations affect risk for sarcoidosis. Objectives of the study of two-year outcome among 240 cases include evaluation of the association of initial category of involvement with category of involvement 24-30 months later; evaluation of clinical presentation, radiographic abnormalities, pulmonary function test results and ancillary data as prognostic indicators; description of indications for therapy; evaluation of outcomes of therapy; and evaluation of the relationship among specific environmental, genetic and socioeconomic factors with the two-year outcome (morbidity and mortality).

A central repository is established to store DNA and plasma specimens for later testing of hypotheses concerning genetic, environmental and occupational factors and infectious agents in the etiology of sarcoidosis. DNA specimens for the repository are prepared in a DNA Core Laboratory according to standardized procedures.

The ACCESS Principal Investigators met in June 1996 to review mini-applications submitted for special laboratory studies. They assigned priorities to the approved studies. Mini-applications submitted and funded are listed in Section 3.6.

3.2 GENETIC FACTORS

Using a case control study design, we will quantify familial aggregation and define risk of sarcoidosis among different classes of relatives. Family history regarding sarcoidosis is obtained from each case and matched control and familial aggregation measured. Affected first degree relatives, who are age 18 years or older and who agree to participate, are interviewed by telephone and their medical records reviewed.

3.3 INFECTIOUS, OCCUPATIONAL AND ENVIRONMENTAL FACTORS

An interviewer-administered occupational / environmental questionnaire is used to obtain information to address the following hypotheses:

1. Sarcoidosis patients (cases) are more likely to report employment in particular occupations or occupational categories when compared with a non-sarcoidosis referent group (controls). The categories considered include:
    - A. Employment in metal dust and metal fume associated industries.
    - B. Employment as health care workers.
    - C. Employment as child care providers and educators.
    - D. Employment as firefighters.
    - E. Employment in the military.
    - F. Employment in agriculture.
    - G. Occupational exposure to organic dusts.
    - H. Employment in mechanically ventilated buildings.
    - I. Employment in environments where exposure to microbial bioaerosols occurs.
    - J. Occupational exposure to chemicals that can produce hypersensitivity pneumonitis or granulomatous lung disease (e.g., isocyanates, pyrethrums).
    - K. Employment indoors.
    - L. Employment in dusty trades.

M. Frequent close contact with co-workers or others during the work day.

2. Sarcoidosis patients (cases) are more likely to report particular environmental exposures when compared with a non-sarcoidosis referent group (controls). The exposures considered include:

   A. Avocational exposure to metal dust and fumes (e.g., welding, jewelry making).

   B. Avocational exposure to children.

   C. Exposure to microbial contamination and bioaerosols in the home environment.

   D. Exposure to organic dusts in a home environment.

   E. Tobacco exposure.

   F. Prior use of medications known to produce hypersensitivity lung diseases or granulomatous disease in other organs.

   G. Rural residence.

   H. Exposure to animal (including bird) antigens.

As part of the occupational and environmental questionnaire, antecedent occupational histories are recorded. Case and control occupations and industries are coded using standardized industrial codes (SIC) and standardized occupational codes (SOC) to test the following hypotheses:

1. Sarcoidosis patients (cases) are more likely to have been employed in certain occupational categories or industries when compared with a non-sarcoidosis referent group (controls).

   Specifically, we propose to test the hypothesis that occupational categories sharing common chemical or biological material exposures confer similar risks of sarcoidosis.

2. Sarcoidosis patients (cases) are more likely to report employment in particular occupations or occupational categories immediately prior to diagnosis of their sarcoidosis conditions when compared to non-sarcoidosis referent group (controls).

3. Sarcoidosis patients (cases) are more likely to have a “dose-related” risk associated with their employment in particular occupational/industrial categories when compared with non-sarcoidosis referent group (controls), based on duration of employment.

Determination of whether or not there is an increased frequency in cases as compared to controls of history of exposures to infectious agents is an important objective of ACCESS. Sarcoidosis may represent a granulomatous response initiated by an environmental, occupational and/or infectious agent.

3.4 SOCIOECONOMIC FACTORS

We are studying how race, socioeconomic status (SES), and medical care use and access are associated with sarcoidosis disease status at presentation and disease progression over time. Specifically, we will test the hypotheses that: sarcoidosis patients will be more likely to be of low SES than controls; sarcoidosis patients with low SES will present with more severe disease and have greater disease progression in two years than patients with high SES; sarcoidosis patients with low SES will have less access to medical services than sarcoidosis patients with high SES; and sarcoidosis patients with low SES will comply less with medical treatment (including adherence to medication), return less regularly for follow-up visits and maintain less continuity of care than patients with high SES. Similar relationships are expected in all racial groups.

3.5 PSYCHOSOCIAL FACTORS AND QUALITY OF LIFE

The impact of sarcoidosis can be measured not only in physical changes, but behavioral, emotional and cognitive outcomes as well. The measurement of these domains reflects an awareness that diseases and their treatment may influence these “quality of life” variables. The physical consequences of sarcoidosis (pain, shortness of breath, changes in appearance, lethargy) and its associated treatment regimens may diminish quality of life by negatively influencing functional status, mood, self-esteem, and interpersonal relations. The impact of sarcoidosis and its associated treatment on a patient’s functional capacity and quality of life has received virtually

no scientific study. Patients report psychosocial dimensions of the disease, such as depression, anxiety, isolation, powerlessness, low self-esteem, poor body image and social issues as key concerns in disease management. Psychosocial and behavioral variables have been shown to be important pre-disposing factors in the etiology of other diseases (e.g., cardiovascular, cancer, diabetes) and to be mediators of disease morbidity and mortality. Given the absence of psychosocial data related to the etiology and course of sarcoidosis, it is timely and cost-effective to incorporate such assessment into this unique study. This project will provide valuable new data in this area. We hypothesize that:

1. Cases with symptomatic disease at baseline will report significantly poorer health-related quality of life and greater depression than healthy community controls.
2. Higher baseline levels of optimism and social support, and lower levels of depression will be associated with higher baseline levels of health-related quality of life in both cases and controls.
3. Baseline levels of depression, social support, and optimism will predict poorer medication adherence and follow-up outcomes, independent of baseline disease severity.

Data to test these hypotheses are collected using the Medical Outcomes Study 36-item Short-Form Health Survey (SF-36), the Center of Epidemiologic Studies Department (CES-D) scale, the Medical Outcomes Study Social Support Scale (MOS-SSS), the Life Orientation Test (LOT) and two study-specific questions concerning medication adherence.

3.6 SPECIAL LABORATORY STUDIES

In June 1996 the ACCESS Principal Investigators set priorities among proposed special laboratory studies to incorporate the highest priority studies in the ACCESS Protocol. Five studies were selected as consistent with the scientific approach in ACCESS and available resources. Progress in each project will be reviewed by the Principal Investigators and DSMB 18 months after the start of support for the special laboratory studies. Progress is assessed based on complete reports on methods development, case and control enrollment, specimen accession, and

preliminary data. Funding for two additional studies was provided by NHLBI in May 1997; progress for these studies will also be reviewed 18 months after the start of funding. Brief descriptions of these studies follow; more detailed descriptions of study methods are found in the ACCESS Procedures Manual Volume IV.

3.6.1 HLA Typing in Sarcoidosis

ACCESS will investigate HLA Class II associations with sarcoidosis and correlate any associations with the environmental history to identify possible causative agents. PCR with sequence specific oligonucleotide (SSO) probes will be used to determine the molecular sequence of HLA Class II DR, DQ and DP beta genes from cases with newly diagnosed sarcoidosis and controls. Any genes that can not be identified using SSO probes will be cloned and sequenced. The specific aims are:

A. Determine which alleles are associated with sarcoidosis and which alleles are protective.

B. Determine which amino acids in the pockets that bind antigenic peptides are associated with sarcoidosis and which are protective.

C. Determine interactions between alleles or amino acids in the binding pockets that are associated with sarcoidosis and specific environmental exposures such as exposure to metals and infectious agents.

D. Determine whether alleles or amino acids in the binding pockets that are associated with sarcoidosis are also associated with specific clinical syndromes (e.g., erythema nodosum, extrapulmonary sarcoidosis, persistent sarcoidosis) among cases.

The case control design is the ideal method to investigate relationships between genetic and environmental factors in disease. Class II molecules are known to be involved in sarcoidosis -- both from the presumed pathophysiology and genetic studies. If specific alleles or amino acids in the binding pockets are found to be associated with sarcoidosis, informative next steps would be immunoprecipitation of Class II molecules with bound antigenic peptide and identification of the

possible etiologic agents that contain those peptides because they may be the etiologic agents of sarcoidosis.

3.6.2 Molecular Analysis of Sarcoidosis-Specific Genes

Building upon the hypothesis that sarcoidosis represents "the response to an exogenous agent in a genetically susceptible individual," this project will use a state-of-the-art molecular biologic technique, the differential display polymerase chain reaction, to identify genes that are expressed in cases with sarcoidosis but not in matched controls. This method provides the opportunity to screen for a wide variety of exogenous agents, such as viral, fungal, and mycobacterial agents as well as previously unidentified organisms. In addition, there is the opportunity to detect candidate endogenous genetic material that is being expressed in cases but not controls, potentially leading to identification of candidate genes which could provide the basis for future genetic studies using molecular epidemiologic approaches.

Initial screening will be performed on 20 cases and 20 controls from one Clinical Center (Beth Israel Deaconess Medical Center) to generate 50 candidate gene markers for sarcoidosis. In order to broaden the opportunity to identify either exogenous or endogenous genetic materials that are preferentially expressed at different times during the natural history of sarcoidosis, there will be no restrictions on the category or stage (Scadding, 1961) of sarcoidosis among cases whose specimens are analyzed. If promising candidate genes are found, an attempt will be made to substantiate the initial findings by performing Northern blot analysis on a different group of 10 cases and 10 controls, using the prioritized gene products. If there are not any promising candidate genes, the initial screening will be extended to include an additional 10 cases and 10 controls.

3.6.3 Searching for an Infectious Etiology for Sarcoidosis

To investigate the hypothesis that sarcoidosis is the result of a response to an infectious agent, the prevalence of micro-organism DNA is determined using broad based PCR for the

detection of 16s-rDNA for micro-organisms in the domain Bacteria, Eukarya and Archaea, in blood samples from both cases and controls.

This project seeks to identify a putative infectious etiology for sarcoidosis by examining blood samples from 100 cases and their matched controls using PCR technology. The broad based infectious organism search uses 16s ribosomal RNA phylogeny; and will examine the 16s-DNA coding the ribosomal RNA. Any DNA that is recovered using this broad-based strategy will be sequenced to determine the possible origin. Preliminary results using broad based primers as well as primers specifically for Mycobacterium tuberculosis have shown that the methodology is applicable to blood samples with a recovery from 100 to 1 organism equivalent per sample.

3.6.4 Role of Mycobacterial Cell Wall Deficient Forms in Sarcoidosis

Since Schaumann's description of "peculiar corpuscles" present in the tissue of patients with sarcoidosis (Schaumann, 1941), an increasing body of evidence has implicated various infectious organisms, particularly mycobacteria, as the etiologic agent(s) in sarcoidosis. Judge, Graham, Khomenko, Barth and Almenoff (Judge and Mattman, 1976; Barth et al, 1979; Khomenko et al, 1987; Graham et al, 1988; Almenoff et al, 1996) have grown mycobacterial cell wall deficient forms (CWDF) from blood and tissue of patients with sarcoidosis. Approximately 80% of patients with sarcoidosis have had cultures positive for CWDF, and fewer than 15% of normal volunteers have had cultures positive for CWDF (Almenoff et al, 1996). However, conflicting results have been obtained using molecular biologic techniques to detect mycobacterial DNA in tissue, broncho-alveolar (BAL) fluid and blood of patients with sarcoidosis. In this study cultures for CWDF are made on 100 cases and 100 controls using techniques already established in the investigator's laboratory, and the species of organism(s) isolated are identified using molecular biologic techniques.

3.6.5 Defining an Etiologic Sarcoid Antigen in the Kveim Reagent

The Kveim-Siltzbach reaction is a localized, delayed granulomatous response to the intradermal injection of sarcoid tissue in patients with sarcoidosis. World-wide, the reaction occurs in 70-80% of individuals with early sarcoidosis and rarely in normal individuals or in other granulomatous disorders. The protracted time course and granulomatous features are strikingly similar to the Mitsuda reaction to lepromins in tuberculous leprosy suggesting that the reaction is due to an unidentified "sarcoid" antigen. Recent studies of T-cell receptor gene expression at sites of Kveim-Siltzbach reactions support the concept that the Kveim reaction is T cell antigen-driven. The goal of this special laboratory study is to establish methods for defining the antigenic component contained in Kveim-Siltzbach reagent that is responsible for its in vivo reactivity in sarcoidosis to test the hypothesis that Kveim-Siltzbach reagent stimulates specific lung and blood T-cell subsets from patients with sarcoidosis. Three specific aims are proposed: determine if bronchoalveolar lavage (BAL) cells from cases are stimulated by validated Kveim reagent; determine if Kveim reagent preferentially stimulates blood mononuclear cells of cases compared with controls; and determine if Kveim-active T-cell lines can be established from the lung or blood of cases and assess the T-cell phenotype of these T-cell lines.

To accomplish these aims, lung and blood T cells are isolated and cultured with validated Kveim reagent and co-stimulating factors such as IL-2 and IL-12. Antigen reactivity is measured by proliferation (^{3}H-thymidine uptake) and cytokine production after various time periods. Long-term T-cell lines with reactivity to Kveim reagent are established for repeated testing of components of Kveim reagent. These T-cell lines are analyzed with respect to T-cell receptors that will also be analyzed in situ in histologic preparations of sarcoid tissue. The development of an in vitro Kveim assay would allow a biochemical analysis of active "sarcoid" antigenic component in Kveim-Siltzbach reagent and potentially define the etiologic agent of sarcoidosis. A power analysis has suggested that six cases and controls would be sufficient to determine whether Kveim reagent

preferentially simulates blood mononuclear cells of cases compared with controls. All cases and controls will be selected from those enrolled at the Johns Hopkins University School of Medicine.

3.6.6 Pathogenic T cells in Sarcoidosis

This project will examine the antigen specificity of the sarcoidosis lung T-cell antigen receptor (TCR). After verifying and sorting important T-cell clones in the lungs of cases (based on serial lavage and on presence of the same clones in lung or lymph node tissue), the investigators propose to sequence both the TCR V-beta and V-alpha partners, insert them into a TCR-deficient murine T-cell hybridoma, and test the ability of these sarcoidosis-specific T cells to respond to putative antigens. The investigators propose similar experiments to be done using normal bronchoalveolar lavage cells and are establishing similar hybridoma lines in “control” disorders, chronic beryllium disease and rheumatoid arthritis, in other projects. Preliminary data from one patient with active sarcoidosis demonstrate the feasibility of the approach, including data showing antigen and mitogen responsiveness of two T-cell hybridomas from this patient. The proposed approach offers a potentially useful in vitro system in which to test putative etiologic agents for antigen specificity. The investigators will study 20 cases who are enrolled at National Jewish Medical and Research Center and have at least one predominant lung T-cell clone.

3.6.7 Immunogenetics of Sarcoidosis

This investigation will identify, map, and determine the mechanism of action of gene(s) responsible for susceptibility to sarcoidosis. The specific aim of this project is to examine the role of candidate loci, such as KM, TNF-á, and IL-1â, in sarcoidosis by comparing specimens from unrelated cases and controls. The role of the genetic markers of immunoglobulins -- KM allotypes -- in sarcoidosis has not been investigated. KM allotypes are excellent candidates for study in sarcoidosis since they are involved in susceptibility to several other immunologically-mediated diseases and they have been shown to influence immune responsiveness to several antigens. In addition to immunoglobulin allotypes, we will also examine the roles of polymorphic loci

which control TNF-á and IL-1â. Increased secretion of these cytokines has been found to be associated with disease severity in sarcoidosis, and the individuals with different alleles at these loci may have different levels of cytokines. For TNF-á, we will examine the two recently described polymorphisms in the promoter region. Both loci involve a G to A transition -- one at position -308 and the other at -238. The fact that these genetic variations are within the promoter region of the TNF-á locus make them likely candidates for regulatory roles in the production of TNF-á. For the determination of the IL-1â alleles, a polymorphic locus in the IL-1â 5' region will be investigated. This polymorphism involves a C to T transition at position -511, which results in an Aval restriction site. All genetic determinations will be done on DNA samples using polymerase chain reaction-based methods. Comparison of KM, TNF-á, and IL-1â phenotype frequencies between cases and controls will be performed, and the interaction of various genetic markers in frequency of occurrence among cases and controls will be assessed. Power calculations have indicated that 360 cases and matched controls will provide sufficient information for these comparisons.

3.7 CONCLUSIONS

ACCESS is a case control study with a limited follow-up of an initial cohort of cases and is designed to collect data to generate specific hypotheses for further investigation concerning genetic, exposure (environmental, occupational and infectious agents), socioeconomic, psychosocial and quality of life factors in the etiology and clinical course of sarcoidosis. Biological specimens collected from cases and controls in ACCESS will be included in special laboratory studies (see Section 3.6). The data from the special laboratory studies will be incorporated with the main ACCESS data to use the detailed ACCESS information in the analysis of the special laboratory study data. Some cases and controls in ACCESS have specimens analyzed in more than one special laboratory study as shown in Table 3-1. When data are available for patients for more than one special laboratory study, these data may be used together in the analysis.

TABLE 3-1

INCLUSION OF ACCESS PATIENTS IN CONCURRENT SPECIAL LABORATORY STUDIES

Special Laboratory Study	HLA Typing in Sarcoidosis	Molecular Analysis of Sarcoidosis-Specific Genes	Searching for an Infectious Etiology for Sarcoidosis	Role of Mycobacterial Cell Wall Deficient Forms in Sarcoidosis	Defining an Etiologic Sarcoid Antigen in Kveim Reagent	Pathogenic T cells in Sarcoidosis	Immunogenetics of Sarcoidosis
HLA Typing in Sarcoidosis	--	X*	X	X	X*	X*	X
Molecular Analysis of Sarcoidosis-Specific Genes		--	X*	X*	0	0	X*
Searching for an Infectious Etiology for Sarcoidosis			--	X	X*	X*	X
Role of Mycobacterial Cell Wall Deficient Forms in Sarcoidosis				--	X*	X*	X
Defining an Etiologic Sarcoid Antigen in Kveim Reagent					--	0	X*
Pathogenic T cells in Sarcoidosis						--	X*

X = Cases and Controls in both studies. 0 = Cases and Controls not included in both studies

*The special laboratory studies Molecular Analyses of Sarcoidosis-Specific Genes, Defining an Etiologic Sarcoid Antigen in Kveim Reagent, and Pathogenic T cells in Sarcoidosis are designed for limited numbers of cases and controls recruited in one (or possibly a few) Clinical Centers. Cases and controls in these smaller studies are expected to be included in the larger special laboratory studies, but the majority of cases and controls in the larger special laboratory studies will not be included in the studies limited to one or a few Clinical Centers.

CHAPTER 4

ADMINISTRATIVE STRUCTURE

4.1 INTRODUCTION

The participating investigators and centers in A Case Control Etiologic Study of Sarcoidosis (ACCESS) collaborate through a study organization that is designed to maintain continuity of operations and to facilitate effective communications and cooperation among the various study units. Exhibit 4-1 summarizes the study administration. The participating centers are listed in Exhibits 4-2, 4-3 and 4-4.

4.2 PARTICIPATING CENTERS

4.2.1 Clinical Centers

Ten Clinical Centers, located at major medical centers/hospitals in the United States, participate in ACCESS. Clinical Centers are responsible for screening and recruitment of eligible sarcoidosis cases and matched controls and collection of all clinical information, specimens, and data required by the ACCESS Study Protocol and transmission of data to the Clinical Coordinating Center.

4.2.2 Clinical Coordinating Center

The Clinical Coordinating Center (CCC) at the Clinical Trials & Surveys Corp. (C-TASC) in Baltimore, Maryland, has primary responsibility for the study's statistical design, data collection and management, and analysis of study results. The CCC staff in cooperation with Clinical Center Investigators developed the Clinical Center Procedures Manual and pretested all study forms. The CCC staff are responsible for preparing and distributing regular ACCESS progress reports and minutes, reports for the Data and Safety Monitoring Board meetings, preparing data bank study analyses, and ensuring the quality and accuracy of data collection. The CCC staff assist in the training of Clinical Center staff in procedures for data collection and transmission of data to the CCC; monitor recruitment of cases and controls; participate in preparation of reports and publications;

provide administrative support in arranging meetings and conference calls; report periodically to the Steering Committee on technical and statistical aspects of the study; develop and implement data processing systems; and monitor progress of the study and quality of the data.

The CCC supervises the activities of the Random Digit Dialing (RDD) Interview Group located at Telesurveys Research Associates. The latter was selected to perform this activity on the basis of review of submissions in response to a Request for Proposals issued by the CCC. The RDD Interview Group is responsible for telephoning households in the local community of the case to identify an individual who is the same gender, age (within five years) and race as the case and who is willing to participate in ACCESS as a matched control.

4.2.3 Central Repository

A Central Repository for storage of case and control biological materials is operated by McKesson Bioservices under contract with the NHLBI.

4.2.4 NHLBI Project Office

The NHLBI Project Office in the Lung Biology and Diseases Program, Division of Lung Diseases is responsible for the overall direction and administration of ACCESS. The Project Office provides general organizational and scientific guidance for the study and monitors the study's progress for the Institute. Epidemiologic and statistical input is provided by representatives from the NHLBI's Division of Epidemiology and Clinical Applications.

4.3 STUDY ADMINISTRATION

4.3.1 Study Chairman

The Study Chairman, appointed by the NHLBI Director, has major responsibility for the scientific direction and administration of ACCESS. The Study Chairman:

1. Advises the NHLBI Project Office on data monitoring and other issues of importance to the overall conduct of the study.

2. Develops and maintains, with advice from other study participants, an internal organizational structure that meets the needs of the study and the NHLBI.
3. Is informed on all aspects of study operations and, using the study organization, formulates study policy and takes action as necessary to insure the smooth operation of the study.
4. Appoints study participants to appropriate positions and committees as needed.
5. Serves as Chairman of the ACCESS Steering Committee and Executive Committee.
6. Serves as an ex-officio, non-voting, member of the Data and Safety Monitoring Board.

The Study Chairman has been appointed to serve for the duration of the study unless other arrangements are made by mutual agreement between the Chairman and the NHLBI Director. In the event that the Study Chairman is unable to serve, the NHLBI Director will appoint a new Chairman.

4.3.2 Study Vice Chairman

The Study Vice Chairman, appointed by the NHLBI Director, assumes the responsibilities of the Study Chairman during the absence of the Study Chairman.

4.3.3 Data and Safety Monitoring Board (External Review Committee)

The Data and Safety Monitoring Board, composed of an independent group of experts in relevant biomedical fields, biostatistics and bioethics, is appointed by the Director, NHLBI. The Study Chairman, Principal Investigator from the Clinical Coordinating Center, and representatives from the NHLBI Project Office also participate as non-voting members. The NHLBI Project Officer serves as the Executive Secretary. The Data and Safety Monitoring Board meets at least twice a year. Its primary role is to advise the NHLBI on all policy matters relating to ACCESS. The Board has responsibility for protecting study participants and monitoring the scientific conduct and integrity of ACCESS in order to assure high quality research. Its functions include:

1. To review and approve the Study Protocol , forms, and Procedures Manual.

2. To review and analyze the progress of the study, and to evaluate its relevance to the program goals.
3. To monitor the study diagnostic procedures for beneficial and adverse effects on the patients.
4. To make recommendations to the NHLBI on major changes in the Protocol, forms, or Procedures Manual. To review and advise NHLBI on ancillary studies (with the possible effect on the main study being the major criterion).
5. To review the quality of the data.
6. To assist the NHLBI in resolution of problems referred by the Steering Committee.
7. To make recommendations to the NHLBI on any proposed early termination of the study because of failure to achieve recruitment goals or adverse or beneficial effects of any study procedure.
8. To recommend remedial measures or discontinuation of individual Clinical Centers which perform unsatisfactorily.

Recommendations made by the Data and Safety Monitoring Board must be approved by the Director of the NHLBI prior to implementation.

4.3.4 Steering Committee

The Steering Committee is composed of the Study Chairman, Principal Investigators from each ACCESS Clinical Center and the Clinical Coordinating Center, and the NHLBI Project Office. This committee provides the scientific direction for the study and meets periodically to assess progress. The Steering Committee is responsible for developing the final Protocol and Procedures Manual and for carrying out the Protocol. Voting Steering Committee members include the Principal Investigator (or designated deputy if the Principal Investigator is not present at the meeting) from each Clinical Center; the Principal Investigator of the Clinical Coordinating Center; the NHLBI Project Officer; and the Study Chairman (if necessary to break a tie). The Study Chairman represents the

Steering Committee on the Data and Safety Monitoring Board. Recommendations by the Steering Committee are subject to ratification by the DSMB and approval by the Director of the NHLBI.

The following technical subcommittees have been established: Background and Rationale; Objectives; Case/Control Selection; Clinical Course; Therapeutic Interventions; Data Analysis; Biological Specimens; Questionnaires; Bronchoalveolar Lavage Procedures; Quality Assurance Procedures; Pulmonary Function Test Procedures. These subcommittees were charged with responsibility for developing specific areas of the ACCESS Protocol and Procedures Manual.

A quorum for a Steering Committee meeting exists when the NHLBI Project Officer is present at the meeting and representatives from each Clinical Center and the Clinical Coordinating Center are also present. All deliberations at the meeting proceed in a parliamentary manner, and Steering Committee decisions are made by a majority vote.

Specific functions of the Steering Committee include:

1. To see that the program policy and Protocol is carried out under the guidance of the NHLBI Project Officer.
2. To review and analyze the progress of the program.
3. To make recommendations to the Data and Safety Monitoring Board concerning changes in the Protocol and Procedures Manual.
4. To review all proposed data bank studies.
5. To review all proposed ancillary studies and to report all recommendations to the Data and Safety Monitoring Board (the major criterion being the possible effect on accomplishing the objectives of the main study).
6. To monitor the performance of the individual Clinical Centers with regard to case and control recruitment and follow-up studies for cases.
7. To monitor the quality of data collected.
8. To be responsible for the presentation of the program results to the biomedical community.

4.3.5 Executive Committee

The Executive Committee is the operational arm of the Steering Committee, and is composed of the Study Chairman, Study Vice Chairman, the Principal Investigator of the Clinical Coordinating Center, the NHLBI Project Officer and two Clinical Center investigators who are elected yearly. The Executive Committee supervises the affairs of the study for the Steering Committee between Steering Committee meetings; and it does not act in conflict with the Steering Committee. This committee has meetings or telephone conference calls or conducts business by mail. The Executive Committee reviews investigator proposed data bank studies (analyses based on the data collected in common by the study investigators), and reviews investigator proposed ancillary studies (based on additional data collected within one or more Clinical Centers in addition to the required study data).

4.3.6 Publications and Presentations Committee

The Publications and Presentations Committee, composed of the study leadership and Principal Investigators from the Clinical Centers, assigns writing and authorship responsibilities for the publication of main results from ACCESS, reviews manuscripts of main results, data bank and ancillary studies as they are prepared for submission for publication, and reviews abstracts prior to submission.

The Publications and Presentations Committee encourages dissemination of the results of ACCESS in high quality publications as well as assures that proposed publications meet criteria regarding patient confidentiality and the appropriateness of presentation of study results. The membership of the NHLBI Project Officer on the Publications Committee ensures compliance with the NHLBI policy that a copy of each article submitted for publication is sent promptly to the Project Officer, that the Project Officer is informed when articles are published, that the Project Officer is furnished a copy of each article published, and that articles published contain the disclosures and disclaimers required by the NHLBI.

EXHIBIT 4-1

ACCESS ADMINISTRATIVE STRUCTURE

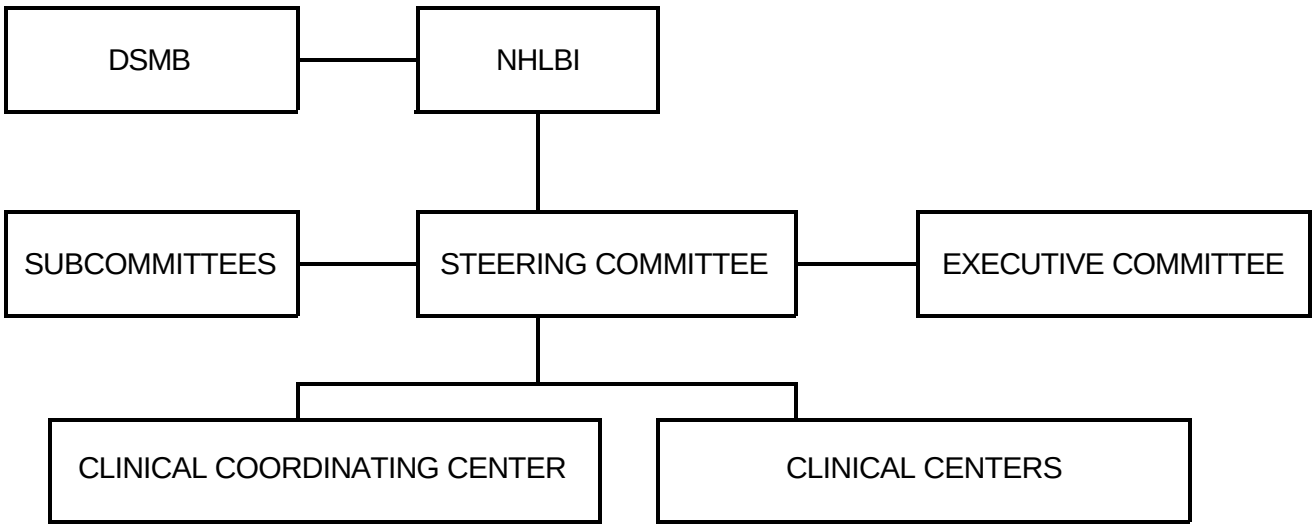

EXHIBIT 4-2

ACCESS CLINICAL CENTERS

1.	Beth Israel Deaconess Medical Center	Boston, Massachusetts
2.	Georgetown University Medical Center	Washington, D.C.
3.	Case Western Reserve University - Henry Ford Health Sciences Center	Detroit, Michigan
4.	Johns Hopkins University School of Medicine	Baltimore, Maryland
5.	Medical University of South Carolina	Charleston, South Carolina
6.	Mount Sinai Medical Center	New York, New York
7.	National Jewish Medical and Research Center	Denver, Colorado
8.	University of Cincinnati	Cincinnati, Ohio
9.	University of Iowa College of Medicine	Iowa City, Iowa
10.	University of Pennsylvania and Allegheny University of the Health Sciences	Philadelphia, Pennsylvania

EXHIBIT 4-3

ACCESS CENTRAL UNITS

Study Chairman

Dr. Reuben Cherniack
National Jewish Medical and Research Center, Denver, Colorado

Study Vice Chairman

Dr. Lee Newman
National Jewish Medical and Research Center, Denver, Colorado

Clinical Coordinating Center

Clinical Trials & Surveys Corp., Baltimore, Maryland

NHLBI Project Office

Lung Biology and Disease Program
Division of Lung Diseases, National Heart, Lung and Blood Institute, Bethesda, Maryland

Central Repository

NHLBI Repository Operated by McKesson Bioservices Under Contract with the Blood Division

Random Digit Dialing Interview Group

Telesurveys Research Associates
Houston, Texas

EXHIBIT 4-4

ACCESS CENTRAL CORE AND SPECIAL STUDIES LABORATORIES

BAL Core Laboratory University of Cincinnati Medical Center	Cincinnati, Ohio
DNA Core Laboratory Case Western Reserve University - Henry Ford Health Sciences Center	Detroit, Michigan
HLA Class II Typing Core Laboratory University of Pennsylvania and Allegheny University of the Health Sciences	Philadelphia, Pennsylvania
Immunogenetics Core Laboratory Medical University of South Carolina	Charleston, South Carolina
Kveim Reagent Special Study Johns Hopkins University School of Medicine	Baltimore, Maryland
L-Forms Core Laboratory Bronx VA Medical Center	Bronx, New York
Pathogenic T Cells in Sarcoidosis Special Study National Jewish Medical and Research Center	Denver, Colorado
Ribosomal RNA Core Laboratory University of Iowa Hospitals and Clinics	Iowa City, Iowa
RNA Core Laboratory Brigham and Women's Hospital	Boston, Massachusetts

CHAPTER 5

POLICY MATTERS

5.1 PUBLICATION POLICY

5.1.1 General Statement of Editorial Policy

It is anticipated that A Case Control Etiologic Study of Sarcoidosis (ACCESS) will generate considerable new data relative to patients with sarcoidosis. The Steering Committee fosters and guides development of scientific reports originating from data obtained in the project. The scientific integrity of the project requires that all data from all Clinical Centers be analyzed study wide and reported as such. Thus, an individual center is expected not to report and publish data collected from its center alone. Development of substudies or data bank studies dealing with specific analyses are encouraged. All presentations and publications of any data collected by the ACCESS Research Group are expected to protect the integrity of the main objectives of the overall project. Major findings are not presented prior to release of "mainline" results of the study by agreement of all ACCESS Principal Investigators. The Steering Committee determines the timing of presentation of mainline results (including papers on design and methods) and designation of the meetings at which they might be presented.

Publications are grouped into six general categories (see Section 5.1.2). Topics for consideration to be developed into publications are generated from questions or hypotheses that are submitted to the Steering Committee by investigators, study coordinators and other study-related staff. A writing group with a designated Chairperson is selected for each topic.

The Publications and Presentations Committee has primary responsibility for reviewing and approving all abstracts and all manuscripts on mainline findings, special laboratory studies, data bank or ancillary studies submitted for presentation or publication. Abstracts and manuscripts are also reviewed by the NHLBI according to existing procedures.

Investigators at all ACCESS Clinical Centers, the Clinical Coordinating Center (CCC), and the NHLBI Project Office have equal status with regard to developing proposals, participating in such

studies as approved by the Steering Committee, and collaborating in the development and publication of research papers based on study material. With the approval of the Principal Investigator, study coordinators and other staff at these centers are encouraged to participate in this process. The Executive Committee has developed standards for regular evaluation of the submission and completion of these protocols. The Executive Committee determines priorities for analyses among data bank study proposals which have been approved.

ACCESS Investigators at Clinical Centers, the CCC or NHLBI proposing studies that require the collaboration of CCC or NHLBI staff (e.g., Central Repository staff) contact the appropriate individuals prior to submission of a given proposal. The appropriate staff in the CCC and NHLBI participate in drafting the proposal, indicate willingness to participate, and identify sources of funding to support the level of effort required for the project.

The CCC Investigators are consulted in the development and analysis of protocols that require review of accumulated data or data on file at the CCC. The members of the CCC and NHLBI Project Office collaborate in designing and carrying out all ACCESS research.

5.1.2 Types of Research

Research and the resulting presentations and publications are grouped into the following categories:

1. Design paper(s) and reports on methodology.
2. Mainline findings.
3. Special laboratory studies.
4. Data bank studies.
5. Ancillary studies.
6. Independent studies.

Distinctions among these types of studies are given in Section 5.2. If possible, analysis of data may be conducted prior to the end of the ACCESS investigation and is strongly encouraged, so that

the maximum information can be published from this study and so that the methods for evaluating and analyzing study data may be refined in preparation for later analyses.

5.1.3 Authorship

The first publication(s) pertaining to the fundamental goals of ACCESS involving cases and controls enrolled in the study will list the“ACCESS Research Group" as the author and list the members of the writing team in a footnote. An appendix listing all Principal and Co-Investigators will be included at the end of the manuscript's text. It is intended that there will also be publications on specific mainline goals, i.e., genetic factors; infections, occupational and environmental factors; socioeconomic factors, and clinical course. These publications will list the writing team as the authors and the last author will be the “ACCESS Research Group.” The authorship for other types of studies are outlined below.

5.1.4 Purpose of Procedural Guidelines

The procedures adopted by the investigators for utilization of study data are intended to protect the interests of all participants in the study, to assure that study data conform to the requirements of study design and are accurately presented, that authorship is appropriately acknowledged, that the text of each publication is well-written, to ensure that all investigators are aware of ongoing analysis projects, to avoid duplication of analysis projects and to ensure that publication or presentation of study data does not occur without the knowledge and approval of the Publications and Presentations Committee and the Steering Committee.

5.2 DESIGN AND METHODS REPORTS, MAINLINE FINDINGS, SPECIAL LABORATORY STUDIES, DATA BANK, ANCILLARY, AND INDEPENDENT STUDIES

5.2.1 Design Papers and Reports on Methodology

Manuscripts concerning the overall design, protocol, procedures, or organizational structure of the study that do not involve mainline findings or data collected on study cases and controls may be published prior to the end of the study. Such preliminary publications will be developed and reviewed according to the same guidelines used for other reports of mainline findings.

Many public presentations about ACCESS that do not involve protocol data, special laboratory studies, data bank or ancillary study data (e.g., grand rounds talks concerning the study's general design and objectives) do not require formal preliminary review and approval by the Publications and Presentations Committee. However, if there is any doubt, investigators are asked to first consult with the Publications and Presentations Committee indicating their intention to present the material, in order to avoid the premature release of study data or the inappropriate publication of confidential information.

5.2.2 Reports of Mainline Findings

A report on mainline findings is one addressing the fundamental goals (as outlined in Chapter 3) of ACCESS or that involves protocol data -- such as changes in pulmonary function or quality of life domains (e.g., depression) over time in sarcoidosis patients -- which cannot be released prior to the end of the study. These studies will summarize the findings based on the entire study population and will be written at the conclusion of the project. These reports must be reviewed and approved by the Publications and Presentations Committee and ratified by the Steering Committee.

5.2.3 Special Laboratory Studies

Five Special Laboratory Studies (HLA Typing in Sarcoidosis; Molecular Analysis of Sarcoidosis-Specific Genes; Searching for an Infectious Etiology for Sarcoidosis; Role of Mycobacterial Cell Wall Deficient Forms in Sarcoidosis; Defining an Etiologic Sarcoid Antigen in Kveim Reagent) were initiated in 1996. Two additional studies (Pathogenetic T-Cells in Sarcoidosis

and Immunogenetics of Sarcoidosis) were initiated in 1997. Reports on these studies will summarize the findings based on the special laboratory study and will be written at the conclusion of each of these studies. These reports must be reviewed and approved by the Publications and Presentations Committee and ratified by the Steering Committee.

5.2.4 Data Bank Studies

A data bank study uses data or specimens (including banked specimens) which are routinely collected on cases or controls who are recruited and/or enrolled in the ACCESS. Analysis of these data are used to answer specific scientific questions. Data used in this research are not directly related to the fundamental goals of the study. Data bank studies must be approved by the Executive Committee and ratified by the Steering Committee. All presentations or publications of data bank studies are to be reviewed following the procedures outlined in Section 5.4.

5.2.5 Ancillary Studies

An ancillary study uses supplementary data that are collected on cases or controls who are recruited and/or enrolled in ACCESS, over and above the data collection required by the protocol. Such studies are restricted to consideration of a specific test technique or involve only the supplemental data collected on study cases and controls. Ancillary studies are reviewed and approved by the Executive Committee and ratified by the Steering Committee prior to initiation to ensure that they do not conflict with the main protocol. Review by the Publications and Presentations Committee is required for presentation or publication of an ancillary study.

5.2.6 Independent Studies

Independent studies of concern to ACCESS are studies conducted in potential cases or controls who are not enrolled in the study, but data are collected at a Clinical Center. These data are not transmitted to the ACCESS Clinical Coordinating Center.

It is understood that each Clinical Center has the right to conduct studies which are independent of ACCESS in patients with sarcoidosis and in potential controls who do not meet criteria for enrollment into the study. Independent studies of cases and controls who meet eligibility criteria but are not enrolled in ACCESS must be reviewed by the Executive Committee. Study investigators agree not to conduct independent studies which would compete with or have a detrimental effect on the conduct of ACCESS during the period of recruitment and follow-up.

5.3 GUIDELINES FOR PREPARATION OF PROPOSALS FOR DATA BANK, ANCILLARY AND SPECIAL LABORATORY STUDIES

5.3.1 Data Bank and Ancillary Studies

Each proposal for an ancillary or data bank study should contain a brief description of the objectives, methods, analysis plans, significance of the study, and proposed collaborators. Full details should be given concerning any procedures to be carried out, such as bronchoalveolar lavage, pulmonary function tests or psychological testing, etc. Mention should be made of any substances to be injected or otherwise administered to the cases and controls. Any observations to be made or procedures to be carried out on cases or controls or on banked specimens outside of the Clinical Center should be described. Mention should be made of the extent to which the data bank or ancillary study requires extra clinic visits or prolongs the usual clinic visits. Information should be given concerning the extent to which the ancillary study require specimens in addition to those presently required by the protocol. If blood specimens are to be obtained from the cases or controls or banked specimens are required, mention should be made of the number of specimens as well as a description of all procedures to be carried out on these specimens.

5.3.2 Special Laboratory Studies

New proposals for special laboratory studies should be prepared in the format of Mini-Applications submitted to the Clinical Coordinating Center for distribution to the Executive Committee for review. Final decision with respect to approval of special laboratory studies will be made by the Steering Committee after formal presentation of the proposal to the Steering Committee.

5.4 PROCEDURES FOR INITIATION AND APPROVAL OF STUDIES

5.4.1 Reports on Mainline Findings

Reports on mainline findings from ACCESS generally involve the collaboration of many investigators. Proposals for these reports are introduced and developed by any ACCESS Investigator or staff member with the approval of the appropriate Principal Investigator. These reports are reviewed and approved by the Executive Committee and ratified by the Steering Committee.

5.4.1.1 Submission of Proposals

Two copies of each proposal should be submitted to the Clinical Coordinating Center for inventory and transmission to the Executive Committee. The Director of the CCC notifies the Investigator when the project is approved, disapproved or whether additional information is needed before a decision can be made.

5.4.1.2 Preparation of Mainline Reports

After approval of a proposed topic for a mainline report, members are elected or invited to serve on an ad hoc Writing Subcommittee and a Chairperson is chosen. These investigators work with the CCC and NHLBI Project Office staff to conduct the data analysis needed to investigate the question at hand and prepare a manuscript based on these findings. Every effort is made by the Subcommittee to consider and incorporate in this manuscript the comments and suggestions from the larger Steering Committee. Often the Subcommittee members meet with staff from the CCC or other Clinical Centers for development of these papers.

5.4.1.3 Review and Approval of Abstracts and Manuscripts Prior to Presentation and Publication

Every study manuscript considered suitable for publication is submitted by the Chairperson of the Writing Subcommittee to the CCC for distribution to the Publications and Presentations Committee. The Chair of the Publications and Presentations Committee is responsible for arranging and implementing review according to the following procedures.

1. The manuscript is forwarded promptly to at least two reviewers selected from the members of the Steering Committee or their associates, with the request to respond within two weeks with a detailed critical review of the manuscript. Outside reviewers are selected when appropriate.
2. Reviews are forwarded to all members of the ad hoc Writing Subcommittee with a request for appropriate revision and response.
3. The ad hoc Writing Subcommittee is expected to respond to the review in a reasonable period of time, forwarding to the CCC the revised manuscript and a letter commenting in detail on the points raised by the reviewers; CCC staff will distribute these materials to the Publications and Presentations Committee.
4. After review by the Publications and Presentations Committee, the CCC staff return the manuscript to the ad hoc Writing Subcommittee with final comments or suggested changes.
5. If acceptable to the study leadership (NHLBI and Executive Committee), the completed manuscript is submitted by the Chairperson of the Writing Subcommittee to the appropriate journal. A copy of the transmittal letter and copy of the manuscript are submitted to the CCC for distribution to the Steering Committee.

5.4.2 Special Laboratory Studies Manuscripts and Abstracts

The Principal Investigator and Co-Investigators of each Special Laboratory Study have primary responsibility for preparing manuscripts and presentations based on the findings of their Special Laboratory Study. It is expected that the Principal Investigator will propose the individuals appropriate

to serve on the Writing Teams of his/her special laboratory study reports. The Executive Committee reviews and approves or makes recommendations regarding alterations in the proposed list of authors for a planned manuscript in advance of initiation of the work on the manuscript.

5.4.3 Data Bank Studies

5.4.3.1 Submission of Proposals

Data bank studies must be approved by the Executive Committee and ratified by the Steering Committee. Before beginning a data bank project, a proposal initiated by one or more of the Investigators and/or their associates is submitted to the CCC for inventory and distribution to the Executive Committee for consideration. The Director of the CCC notifies the Investigator when the project is approved, disapproved or additional information is needed before a decision can be made.

5.4.3.2 Conduct of Data Bank Studies

After approval is given by the Steering Committee, the Principal Investigators (on the data bank project) work with the CCC and NHLBI Project Office staff to conduct the data analysis.

5.4.3.3 Priorities for Work

Because of the routine work load at the CCC, it is necessary to establish priorities for data processing and analysis. Therefore, the CCC staff conduct analyses on data bank studies in the order in which they have been approved or, as necessary, seek guidance from the Executive Committee for determining priorities for analysis.

5.4.3.4 Authorship

After a data bank study proposal is approved by the Steering Committee, its research and development are the responsibility of the identified investigators on the project. Authorship decisions on data bank studies take into account the unique cooperative effort that has produced the results. For clinical papers in particular, individuals from Clinical Centers, CCC, and NHLBI staff have the opportunity to join writing teams when their contributions are appropriate. On the other hand, there will be papers of more limited scope which probably do not warrant a large number of authors. The following mechanism is utilized to determine authorship:

1. The lead author proposes a list of co-authors, based on the above guidelines.
2. The Executive Committee reviews and approves, or makes recommendations regarding alterations in the proposed list of authors.

   The names of these investigators is followed by the designation "and ACCESS Research Group" on the byline.

5.4.3.5 Review and Approval of Abstracts and Manuscripts Prior to Presentation or Publication

The Publications and Presentations Committee reviews all data bank study abstracts and manuscripts prior to submission for presentation and publication. Recommendations are forwarded to the Executive Committee for review and final decision. All abstracts must be received by the Publications and Presentations Committee members, all co-authors, and CCC at least two weeks prior to the submission deadline. Manuscripts prepared based on data bank studies must be submitted to the CCC at least one month (30 days) before the scheduled submission date. After review, the Publications and Presentations Committee makes recommendations to the Executive Committee in consultation with the CCC. The Director of the CCC notifies the authors and Steering Committee of the decision within one month of the receipt of a manuscript, within one week for abstracts. The approved manuscript or abstract is then submitted.

5.4.4 Ancillary Studies

5.4.4.1 Submission of Proposals

Ancillary study proposals are reviewed by the Executive Committee and are ratified by the Steering Committee to ensure that the proposed study does not conflict with the primary goals of ACCESS.

Two copies of each proposal are submitted to the Clinical Coordinating Center for inventory and transmission to the Executive Committee. The Director of the CCC notifies the Investigator when the project is approved, disapproved or additional information is needed before a decision can be made.

Abstracts and manuscripts are to be submitted for review prior to submission.

5.4.5 Independent Studies

Results of independent studies which are approved as acceptable by the Executive Committee may be published or presented at the discretion of investigators initiating the independent study.

5.5 RELEASE OF ACCESS DATA OR SPECIMENS TO NON-ACCESS INVESTIGATORS

Requests for study results, study data, or banked specimens may be submitted by investigators who are not participating in ACCESS during the course of this investigation. These requests will arise primarily from colleagues and researchers who are interested in sarcoidosis. Each request should be submitted in writing and provide the same information as required for study data bank and ancillary studies submitted by ACCESS Investigators. The Executive Committee reviews each request and the following principles are addressed in determining the disposition of each request .

1. Overlap with the study major goals or approved data bank and ancillary studies.
2. The scientific importance of the request.
3. The efforts and costs of providing the information.

4. The willingness of the individuals submitting the request to accept the limitations, as specified by the ACCESS Executive Committee, on the uses that can be made of the data and data analysis.

After all funding for ACCESS has ended a special review group appointed by the NHLBI will serve in the capacity of the Executive Committee to review requests for the use of the remaining banked specimens stored in the Central Repository. This review group will be responsible for reviewing requests from study ACCESS Investigators as well as non-ACCESS Investigators and making a recommendation to the NHLBI and staff at NHLBI will make the final decision. The decision for release of the specimens will be based on the availability of specimens, the scientific goals of the proposal and the order the requests are received after public notice has been issued to announce the availability of the specimens and the NHLBI Policy on Release of Specimens.

At least one month prior to the end of funding, the Clinical Coordinating Center staff will prepare data tapes and appropriate documentation for submission to the NHLBI Project Office. These tapes will not include personal identifiers of either cases or controls. The documentation will include the information necessary to link stored specimens to individual case and control data if the case or control specified at the time of enrollment that his/her specimen could be used for non-ACCESS related research. The release of these data tapes will be based on the NHLBI Policy on Release of Data from Large Scale NHLBI Sponsored Studies in existence at the time the study funding ceases.

5.6 CONFLICT OF INTEREST POLICY

5.6.1 General Principles

The ACCESS investigators have agreed to a policy on conflict of interest which has few specific restrictions, but a broad indication for disclosure of potential conflicts of interest. The ACCESS investigators wish to endorse the spirit and content of the 21st Bethesda Conference: Ethics in Cardiovascular Medicine (Frommer et al, 1990) dealing with these issues, and seek to make this policy consistent with the record of that conference.

To address actual or perceived conflict of interest in ACCESS, the participating investigators voluntarily agree to abide by the guidelines described in the policy statement developed for ACCESS. See Exhibit 5-1 for a copy of the Conflict of Interest Statement.

5.6.2 Individuals to be Governed by These Guidelines

Members of the ACCESS Study Group who will be governed by these guidelines include the Study Chairman, the Principal Investigator at each Clinical Center, key personnel in the Clinical Coordinating Center, and the Principal Investigators of the Core Laboratories. Co-Investigators and other staff who have major responsibility for enrollment, recruitment, follow-up or collection of data for ACCESS at Clinical Centers or Core Laboratories will also be governed by these guidelines. The Principal Investigator for each ACCESS Center will submit a list of individuals who will be governed by these guidelines at the beginning of the study and revise, as necessary, annually. The Principal Investigator of each participating unit will review the guidelines with all appropriate staff prior to the start of patient recruitment and at least annually thereafter.

5.6.3 Time Period of the Policy

The guidelines set forth in this policy commence at the start of patient recruitment and will terminate at the time of initial public presentation or publication of the principal results. Investigators not privy to end point data who discontinue participation in the study during recruitment will be subject to these guidelines until their departure from the study.

5.6.4 Financial Guidelines

1. The investigators agree not to own, buy or sell stock or stock options during the aforementioned time period in any of the pharmaceutical companies or related medical equipment companies with products used in this study, or who have provided financial support for the study. In addition, the investigators agree not to have retainer-type consultant positions with these companies for the time period defined above.

2. The Clinical Coordinating Center will maintain conflict of interest statements updated annually from each investigator.

Activities not explicitly prohibited, but to be reported annually and maintained by the Clinical Coordinating Center include:

1. Ad hoc consultant relationships to companies providing products or equipment used in the study or providing financial support to the study.
2. Participation of investigators in any educational activities that are supported by the companies defined above.
3. Participation of investigators in other research projects supported by the companies defined above.
4. Financial interests in the companies defined above, over which the investigators has no control, such as mutual funds or blind trusts.

5.6.5 Reporting of Financial Disclosures and Other Activities

The investigators agree to update their financial disclosures and related activities as described above on an annual basis and submit these data to the Clinical Coordinating Center for storage. The Clinical Coordinating Center staff maintain the confidentiality of these records and prepare any reports indicating a potential conflict of interest for review by the Executive Committee. In the case of actual or perceived conflict of interest, the Study Chairman brings it to the attention of the Executive Committee, NHLBI Project Office, and the Data and Safety Monitoring Board.

5.6.6 Review of Policy Statement

The investigators agree to review these guidelines on an annual basis and take any additional steps to insure that the scientific integrity of the study remains intact.

5.6.7 Relationship to Institutional Policies on Conflict of Interest

Since existing policies on conflict of interest vary among participating institutions, in addition to the above policy, it is expected that investigators comply with the policies on conflict of interest

which exist within their individual participating institutions (medical schools and hospitals). This is the responsibility of each individual investigator.

5.7 ACKNOWLEDGMENT OF NON-FEDERAL FUNDING

In the reports on major findings, data bank and ancillary studies, the financial support of all non-federal groups will be acknowledged at the end of each manuscript.

EXHIBIT 5-1

CONFLICT OF INTEREST STATEMENT
FOR ACCESS INVESTIGATORS

CONFIDENTIAL

Except as noted below:

CI am not a part-time, full-time, paid or unpaid employee of any organizations:

(a) whose products or services will be used or tested in the study under review, or (b) whose products or services would be directly and predictably affected in a major way by the outcome of the study;

CI am not an officer, member, owner, trustee, director, expert advisor, or consultant of such organizations; and

CI do not have any financial interests or assets in any organizations meeting the above criteria, nor does my spouse, dependent children, nor organizations with which I am connected.

PLEASE COMPLETE THE APPROPRIATE BOX BELOW.

9 NO RELEVANT INTERESTS OR ACTIVITIES.
9 EXCEPTIONS ARE NOTED IN THE ATTACHED LETTER.

I will notify the Clinical Coordinating Center Principal Investigator promptly if:

Ca change occurs in any of the above during the tenure of my responsibilities, or
CI discover that an organization with which I have a relationship meets the criteria for a conflict of interest.

I am aware of my responsibilities for maintaining the confidentiality of any non-public information that I receive or become aware of through this activity, and for avoiding using such information for my personal benefit, the benefit of my associates, or the benefit of organizations with which I am connected or with which I have a financial involvement.

_____ _____
Investigator (type name) Signature

_____
Date

CHAPTER 6

CASE AND CONTROL SELECTION

6.1 CASE DEFINITION

All cases should have a clinical course compatible with sarcoidosis, that is, a systemic granulomatosis of unknown etiology. All cases selected for inclusion in the study have tissue confirmation of granuloma. The Kveim test may be used to confirm a diagnosis of sarcoidosis in patients with Löfgren's Syndrome (defined by the presence of erythema nodosum), if no other tissue is obtained. Kveim agent may be used for tissue confirmation only in cases with Löfgren's Syndrome. Investigators using the Kveim agent must adhere to the U.S. Food and Drug Administration (FDA) Investigational New Drug (IND) Application requirements for use of this agent. Standardized procedures for interpretation of the Kveim biopsies are described in the IND documentation and the ACCESS Procedures Manual Volume I.

Intrathoracic disease documented by mediastinal lymph node or transbronchial biopsies does not require clinical evidence of other organ involvement. A patient with a positive biopsy of a skin lesion requires involvement of at least one other organ as defined in Table 6-1. Table 6-1A provides the categories in use starting November 1996. Revisions to this table were made in April 1998 (Table 6-1B), but did not change the diagnostic criteria. Cases with uveitis on slit lamp examination require a biopsy of other involved tissue.

Tissue samples are considered positive for sarcoidosis if they demonstrate non-caseating granuloma and are read as being compatible with a diagnosis of sarcoidosis, without other possible causes. All biopsies are reviewed by a single pathologist at each Clinical Center for quality control purposes. The Clinical Center Principal Investigator reports the pathologist's level of certainty of the diagnosis of the presence of granuloma as definite, possible, and clearly not. If the tissue is interpreted as a possible or probable diagnosis, the Clinical Coordinating Center identifies pathologists at other Clinical Centers who review the slides (including special stains) in question as an unknown sample as part of the quality control program.

Multiorgan disease is defined as tissue confirmation in at least one organ, and either clinical or pathological involvement in another organ(s), as outlined in Table 6-1. The record of organ involvement for cases is based on abnormalities ever observed in the set of definitions in use November 1996 - March 1998, and in the revised definitions in use starting April 1998. The revisions made to the criteria for organ involvement in April 1998 were clarifications of wording, deletion of evidence of treatment response as a criterion (because almost none of the ACCESS cases have had a definitive course of treatment at the time of study entry and some of these abnormalities may respond to the same treatment if used for other diseases), and regrouping of the categories into those that are common, those that are unusual but serious, and other organ involvement.

Individuals with chronic beryllium disease are excluded from the study. Potential cases with occupational histories indicating possible beryllium exposure are excluded from the study unless both blood and bronchoalveolar lavage proliferation studies indicate a negative response to beryllium. Fungal lung disease and tuberculosis should be ruled out. Specifically, all cases should have acid-fast bacillus (AFB) and fungal cultures of all available tissue performed and appropriately stained unless the diagnosis was confirmed by the Kveim agent. In potential cases undergoing bronchoscopy, bronchial washings should always be obtained specifically for fungal and AFB cultures. Potential cases who live in areas where histoplasmosis is endemic or who have risk factors for tuberculosis should have appropriate tests performed on tissue specimens (cultures of biopsy specimens required) to exclude tuberculosis and fungal infections (especially histoplasmosis). In particular, adequate samples should be cultured, if possible. At a minimum, slides of tissue should be stained for mycobacteria and fungi. Fungal serology and measures of *H. capsulatum* antigen are not expected to contribute to the diagnosis and are not used in ascertaining case eligibility. All slides for cases enrolled after September 1997 are reviewed under polarized light to determine whether birefringent material is present. A review for birefringent material on the slides of cases enrolled prior to September 1997 is performed if the slides are available.

At least four transbronchial biopsy specimens are recommended for patients whose tissue diagnosis is approached with bronchoscopy and transbronchial biopsy. In patients who have an

atypical presentation for sarcoidosis, such as asymmetrical hilar adenopathy or asymmetrical pulmonary infiltrates, a sufficient amount of tissue must be sampled. For patients undergoing mediastinoscopy, it should be determined prior to the procedure which lymph nodes are considered abnormal so that biopsies of those nodes can be obtained rather than normal sized lymph nodes. Biopsy should be obtained of a grossly enlarged lymph node ($\geq$ 2 cm) and not of normal sized lymph nodes.

Only newly diagnosed cases are enrolled in the study. Newly diagnosed cases are of interest for accuracy and consistency of recall. A newly diagnosed case is defined as a patient who has had tissue confirmation less than six months prior to entry into the study. Cases may have received systemic treatment for sarcoidosis during this period. The day of the biopsy that confirms the presence of sarcoidosis is defined as the day of diagnosis. Duration of symptoms or findings are noted, and this information is used in comparison of cases and controls.

All cases have a baseline evaluation including an administered questionnaire, medical history and physical examination, postero-anterior (PA) chest X-ray; tissue documentation of disease; biochemistry panel which includes total protein, albumin, alkaline phosphatase, aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, serum urea nitrogen, calcium and creatinine; complete blood count with a differential; and spirometry (with bronchodilators if clinically indicated). Additional desirable, but not mandatory, studies include angiotensin converting enzyme assay (an inexpensive measure of disease activity, but not implicated in etiologic hypotheses); slit-lamp examination conducted by an ophthalmologist; purified protein derivative (PPD) skin test; lung volumes and single breath diffusing capacity. If patients were diagnosed elsewhere, pre-treatment biochemistry and complete blood count data from specimens at the time of diagnosis may be recorded as the baseline tests.

6.2 CASE SELECTION

It is planned that the total study population will consist of 720 cases and 720 controls. Each Clinical Center enrolls, interviews, examines and collects blood specimens from 72 cases with

sarcoidosis and enrolls, interviews and collects blood specimens from 72 matched controls during the recruitment period (November 1, 1996 through June 30, 1999).

Cases may be recruited from a variety of clinical settings, including inpatient, hospital-based outpatient, and non hospital-based outpatient. Each Principal Investigator defines, in advance, the geographic area from which the center recruits patients for the study. Permission to contact patients identified in a clinical setting must be obtained initially from the attending physician of record, in advance of study enrollment. Potential cases are informed that a payment will be given to reimburse them for parking costs, meals and other expenses (including lost time from work) at the medical center, and transportation costs.

At the time of enrollment into the study, patients are categorized according to their clinical condition at the time of initial diagnosis, i.e., the day of biopsy confirmation. Table 6-2A outlines the disease categories that were used to describe cases beginning November 1996. An additional revised classification system was used beginning September 1997 and is given in Table 6-2B. The purpose of revising the disease categories is to encourage use of information on facets of the clinical presentation of sarcoidosis that were not readily appreciated in the hierarchical, initial classification of disease categories. This information is used in ACCESS to assess the spectrum of clinical sarcoidosis presentations represented among the ACCESS cases.

Initially cases are recruited at each participating Clinical Center sequentially without regard to the proportion in each category. If cases are identified from more than one patient source (e.g., different clinics or practices) within the Clinical Center, efforts are made to enroll every patient from each patient source over the period of the study year. Clinical Coordinating Center staff review the distribution of enrolled cases periodically to ensure that appropriate proportions of cases in each category are enrolled by the end of the recruitment period. Assessment occurs after each 150 incident cases have been enrolled in the study. Based on each analysis, Clinical Centers may be required to adjust the proportion of cases recruited for each category.

Clinical Center Coordinators complete screening logs for data entry and submission to the Clinical Coordinating Center. Cases are considered potential participants if their records show they

satisfy sarcoidosis eligibility criteria. Those deemed eligible are invited to participate in the study. For those cases who are ineligible for further consideration in ACCESS no questionnaire data will be collected. Data collected on those who are ineligible or refuse to participate in the study include basic demographics (age, race, gender), type of health care coverage (private insurance, managed care, no insurance, Medicare, Medicaid), and reasons for ineligibility or refusal to participate. Completion of screening logs for cases was discontinued in October 1997.

6.3 CONTROL SELECTION

There is one population-based control group, selected for the study through random digit dialing. Controls are matched to cases on age (within five years), gender and self-designated race (black, white, other).

6.3.1 Random Digit Dialing Controls

Cases are matched in a one to one ratio to controls selected through random digit dialing. Random digit dialing facilitates the selection of a control group that approximates a probability sample in the population. Random digit dialing (RDD) is used to identify potential controls through an unbiased clustered random sample of households with telephones (Waksberg, 1978). Cluster sampling of telephone households and a stratified sample of age-, gender-, and self-identified race-matched individuals are used (Hartge et al, 1984).

The groups selected to generate telephone numbers, Survey Sampling Inc. (SSI), and to perform the telephone recruitment of potential controls, Telesurveys Research Associates (Random Digit Dialing (RDD) Interview Group), work under the direction of the Clinical Coordinating Center. The RDD callers are responsible for making initial telephone contact with potential controls in the geographic areas of the Clinical Centers.

Once the RDD Interview Group recruiter has established the eligibility, availability and willingness of the potential control to participate, the potential control is informed that an interviewer from the Clinical Center will be in touch soon to set up an appointment to meet for questionnaire

administration and phlebotomy. Potential controls are informed that a payment will be given to them after they complete the study interview to reimburse them for parking costs, meals and other expenses (including lost time from work) at the medical center, and transportation costs.

RDD Interview Group sends the name, address and telephone number by facsimile transmission to the Clinical Center and the Clinical Coordinating Center. As soon as possible the potential control is called back by Clinical Center staff to confirm that the potential control is eligible and is still interested in participating in ACCESS. At the same time as efforts are being made to contact the potential case by telephone, a letter on the medical center letterhead is sent to the potential control. If the individual agrees, Clinical Center staff arrange an appointment for an interview at the Clinical Center or another mutually acceptable location. Once the interview and phlebotomy have been completed, the Clinical Center notifies the Clinical Coordinating Center that the match has been completed. If the potential control refuses to comply with the study requirements or is ineligible, the Clinical Center notifies the Clinical Coordinating Center that another potential RDD control should be identified. For potential controls who are ineligible or refuse to participate, reasons for ineligibility or refusal are recorded and, if feasible, information on type of health care coverage is collected.

6.4 INCLUSION/EXCLUSION CRITERIA AND CONFIRMATION OF ELIGIBILITY

Only patients 18 years of age or older may be enrolled in the study. Patients cannot have active tuberculosis or be taking anti-tuberculosis therapy. Potential controls with a past history of sarcoidosis, chronic beryllium disease, fungal diseases treated with systemic chemotherapy, granulomatous hepatitis, primary biliary cirrhosis, Bell's palsy, uveitis, Crohn's disease, and erythema nodosum of unknown etiology are excluded from the study.

Potential cases and controls must be competent to sign consent forms for study participation and must be willing to participate for the length of the study. They may be excluded from the study if there is evidence that they may not comply with all study requirements. Potential cases and controls must be able to respond directly to questions on the study forms to be eligible for inclusion in the study.

The eligibility of potential cases and controls is determined by the Clinical Center Coordinator through a combination of record review and telephone and personal interview. The Coordinator explains the nature of ACCESS to the potential cases and controls. If the potential case or control is interested in participating in ACCESS, the Coordinator administers a brief structured questionnaire addressing eligibility issues not gleaned from the medical record or telephone interview.

Potential cases and controls who are eligible and agree to enrollment, are asked to sign one or more consent forms to participate, depending upon the individual's case/control status (see Chapter 7). Cases and controls are identified only by a patient name code and identification number. The patient's name code and identification number serve to conceal the personal identity from the ACCESS Clinical Coordinating Center and Clinical Center staff and to maintain confidentiality. The patient's name code and identification number are recorded on separate ACCESS logs for cases and controls. These logs include the following information:

1. Date of initial contact.
2. Age.
3. Gender.
4. Race.
5. Health care coverage.

The reasons for ineligibility are recorded for all cases and controls deemed ineligible to participate in ACCESS. As noted in Section 6.2 completion of screening logs for cases was discontinued in October 1997.

6.5 INTERVIEWS

Trained individuals interview all patients in an outpatient setting. Patients identified at the time of hospitalization are interviewed at the first feasible outpatient follow-up visit. The interview is conducted only after informed consent has been obtained. Cases and controls are informed that the focus of the study is to determine the cause(s) of sarcoidosis. Masking of the interviewers to individual status as a case or control is not planned.

TABLE 6-1A

MULTI-ORGAN INVOLVEMENT IN PATIENTS WITH BIOPSY–CONFIRMED SARCOIDOSIS USED BEGINNING NOVEMBER 1996

DEFINITION OF ORGAN INVOLVEMENT: 1) Positive biopsy of the organ or one of the clinical conditions in Table 6-1. 2) No other cause identified (such as infection, trauma, pre-existing condition, or co-existing disease). 3) Treatment for sarcoidosis such as corticosteroids, azathioprine chloroquine, or methotrexate associated with improvement in organ function.

ORGAN	DEFINITE	PROBABLE	POSSIBLE
NEUROLOGIC	1. Positive MRI with uptake in meninges or brainstem 2. CSF with increased lymphocytes and/or protein 3. Diabetes insipidus 4. Bell's Palsy 5. Cranial nerve dysfunction 6. Peripheral nerve biopsy	1. Other abnormalities on MRI 2. Unexplained neuropathy 3. Positive EMG	1. Unexplained headaches 2. Peripheral nerve radiculopathy
NON-THORACIC LYMPH NODE		1. New palpable node above waist 2. Lymph node > 2 cm by CT scan	1. New palpable femoral lymph node
RENAL	1. Treatment responsive renal failure	1. Steroid responsive renal failure in patient with diabetes and/or hypertension	1. Renal failure in absence of other disease
LUNGS	1. Chest roentgenogram with one of the following: -Bilateral hilar adenopathy -Diffuse infiltrates -Upper lobe fibrosis 2. Restriction on PFTs	1. Lymphocytic alveolitis by BAL 2. Any pulmonary infiltrates 3. Isolated reduced DLCO	1. Any adenopathy 2. Obstructive PFTs
CARDIAC	1. Treatment responsive cardiomyopathy 2. EKG showing IVCD or nodal block 3. Positive gallium scan of heart	1. No other cardiac problem and either: -Ventricular arrhythmias -Cardiomyopathy 2. Positive thallium scan	1. In patient with diabetes and/or hypertension: -Cardiomyopathy -Ventricular arrhythmias

TABLE 6-1A (Continued)

MULTI-ORGAN INVOLVEMENT IN PATIENTS WITH BIOPSY–CONFIRMED SARCOIDOSIS USED BEGINNING NOVEMBER 1996

DEFINITION OF ORGAN INVOLVEMENT: 1) Positive biopsy of the organ or one of the clinical conditions in Table 6-1. 2) No other cause identified (such as infection, trauma, pre-existing condition, or co-existing disease). 3) Treatment for sarcoidosis such as corticosteroids, azathioprine chloroquine, or methotrexate associated with improvement in organ function.

ORGAN	DEFINITE	PROBABLE	POSSIBLE
SKIN	1. Lupus pernio 2. Annular lesion	1. Macular papular lesions 2. New nodules	1. Keloids 2. Hypopigmentation 3. Hyperpigmentation
EYES	1. Lacrimal gland swelling 2. Uveitis 3. Optic neuritis	1. Blindness	1. Glaucoma 2. Cataract
LIVER	1. LFTs > three times normal	1. Compatible CT scan 2. Elevated alkaline phosphatase	
BONE MARROW	1. Granulomas in bone marrow 2. Unexplained anemia 3. Leukopenia 4. Thrombocytopenia		1. Anemia with low MCV
SPLEEN		1. Enlargement by: -Exam -CT scan -Radioisotope scan	
BONE / JOINTS	1. Granulomas in bone biopsy 2. Cystic changes on hand or feet phalanges	1. Asymmetric, painful clubbing	1. Arthritis with no other cause
EAR / NOSE / THROAT	1. Granulomas in ear, nose or throat	1. Unexplained hoarseness with exam ~~,~~ consistent with granulomatous involvement	1. New onset sinusitis 2. New onset dizziness

TABLE 6-1A (Continued)

MULTI-ORGAN INVOLVEMENT IN PATIENTS WITH BIOPSY–CONFIRMED SARCOIDOSIS USED BEGINNING NOVEMBER 1996

DEFINITION OF ORGAN INVOLVEMENT: 1) Positive biopsy of the organ or one of the clinical conditions in Table 6-1. 2) No other cause identified (such as infection, trauma, pre-existing condition, or co-existing disease). 3) Treatment for sarcoidosis such as corticosteroids, azathioprine chloroquine, or methotrexate associated with improvement in organ function.

ORGAN	DEFINITE	PROBABLE	POSSIBLE
PAROTID / SALIVARY GLANDS	1. Biopsy confirmation 2. Symmetrical parotitis with syndrome of mumps 3. Positive gallium scan (“Panda sign”)		1. Dry mouth
MUSCLES	1. Granulomas in muscle 2. Increased CPK/aldolase which decreases with treatment	1. Increased CPK/aldolase	1. Myalgias responding to treatment
HYPERCALCEMIA / HYPERCALCURIA / NEPHROLITHIASIS	1. Increased serum calcium with no other cause	1. Increased urine calcium 2. Nephrolithiasis analysis showing calcium	1. Nephrolithiasis - no stone analysis 2. Nephrolithiasis with negative family history for stones

MRI = magnetic resonance image; CSF = cerebrospinal fluid; EMG = Electromyogram; CT = computed tomography;
PFTs = pulmonary function tests; DLCO = diffusing capacity of the lungs for carbon monoxide; BAL = bronchoalveolar lavage;
EKG = electrocardiogram; IVCDs = interventricular conduction defect ; LFT = liver function test; MCV = mean corpuscular volume

TABLE 6-1B

CRITERIA FOR ORGAN INVOLVEMENT IN PATIENTS WITH BIOPSY–CONFIRMED SARCOIDOSIS
COMMON INVOLVEMENT
USED BEGINNING APRIL 1998

DEFINITION OF ORGAN INVOLVEMENT: 1) Positive biopsy documents definite involvement of the organ; 2) Involvement according to criteria other than biopsy is classified as definite, probable or possible on the basis of clinical evaluation (described in the table below for each organ) and assumes no other cause identified (such as infection, trauma, pre-existing condition, or co-existing disease).

ORGAN	DEFINITE	PROBABLE	POSSIBLE
LUNGS	1. Chest roentgenogram with one or more of the following: -Bilateral hilar adenopathy -Diffuse infiltrates -Upper lobe fibrosis 2. Restriction on pulmonary function tests	1. Lymphocytic alveolitis by bronchoalveolar lavage (BAL) 2. Any pulmonary infiltrates 3. Isolated reduced diffusing capacity for carbon monoxide	1. Any adenopathy 2. Obstructive pulmonary function tests
SKIN	1. Lupus pernio 2. Annular lesion	1. Macular/ papular 2. New nodules	1. Keloids 2. Hypopigmentation 3. Hyperpigmentation
EYES	1. Lacrimal gland swelling 2. Uveitis 3. Optic neuritis	1. Blindness	1. Glaucoma 2. Cataract
LIVER	1. Liver function tests > three times normal	1. Compatible computer tomography (CT) scan 2. Elevated alkaline phosphatase	
HYPERCALCEMIA / HYPERCALCURIA / NEPHROLITHIASIS	1. Increased serum calcium with no other cause	1. Increased urine calcium 2. Nephrolithiasis analysis showing calcium	1. Nephrolithiasis - no stone analysis 2. Nephrolithiasis with negative family history for stones

TABLE 6-1B (Continued)

CRITERIA FOR ORGAN INVOLVEMENT IN PATIENTS WITH BIOPSY–CONFIRMED SARCOIDOSIS
UNUSUAL, BUT SERIOUS COMPLICATIONS
USED BEGINNING APRIL 1998

DEFINITION OF ORGAN INVOLVEMENT: 1) Positive biopsy documents definite involvement of the organ; 2) Involvement according to criteria other than biopsy is classified as definite, probable or possible on the basis of clinical evaluation (described in the table below for each organ) and assumes no other cause identified (such as infection, trauma, pre-existing condition, or co-existing disease).

ORGAN	DEFINITE	PROBABLE	POSSIBLE
NEUROLOGIC	1. Positive magnetic resonance imaging (MRI) with uptake in meninges or brainstem 2. Cerebrospinal fluid with increased lymphocytes and/or protein 3. Diabetes insipidus 4. Bell's Palsy 5. Cranial nerve dysfunction 6. Peripheral nerve biopsy	1. Other abnormalities on magnetic resonance imaging (MRI) 2. Unexplained neuropathy 3. Positive electromyogram	1. Unexplained headaches 2. Peripheral nerve radiculopathy
RENAL	1. Treatment responsive renal failure	1. Steroid responsive renal failure in patient with diabetes and/or hypertension	1. Renal failure in absence of other disease
CARDIAC	1. Treatment responsive cardiomyopathy 2. Electrocardiogram showing intraventricular conduction defect or nodal block 3. Positive gallium scan of heart	1. No other cardiac problem and either: -Ventricular arrhythmias -Cardiomyopathy 2. Positive thallium scan	1. In patient with diabetes and/or hypertension: -Cardiomyopathy -Ventricular arrhythmias

TABLE 6-1B (Continued)

CRITERIA FOR ORGAN INVOLVEMENT IN PATIENTS WITH BIOPSY–CONFIRMED SARCOIDOSIS
OTHER ORGAN INVOLVEMENT
USED BEGINNING APRIL 1998

DEFINITION OF ORGAN INVOLVEMENT: 1) Positive biopsy documents definite involvement of the organ; 2) Involvement according to criteria other than biopsy is classified as definite, probable or possible on the basis of clinical evaluation (described in the table below for each organ) and assumes no other cause identified (such as infection, trauma, pre-existing condition, or co-existing disease).

ORGAN	DEFINITE	PROBABLE	POSSIBLE
NON-THORACIC LYMPH NODE		1. New palpable node above waist 2. Lymph node > 2 cm by computer tomography (CT) scan	1. New palpable femoral lymph node
BONE MARROW	1. Unexplained anemia 2. Leukopenia 3. Thrombocytopenia		1. Anemia with low mean corpusclar volume (MCV)
SPLEEN		1. Enlargement by: -Exam -Computer tomography (CT) scan -Radioisotope scan	
BONE / JOINTS	1. Cystic changes on hand or feet phalanges	1. Asymmetric, painful clubbing	1. Arthritis with no other cause
EAR / NOSE / THROAT		1. Unexplained hoarseness with exam consistent with granulomatous involvement	1. New onset sinusitis 2. New onset dizziness
PAROTID / SALIVARY GLANDS	1. Symmetrical parotitis with syndrome of mumps 2. Positive gallium scan (“Panda sign”)		1. Dry mouth
MUSCLES	1. Increased creatine phosphokinase (CK)/aldolase which decreases with treatment	1. Increased creatine phosphokinase (CK)/aldolase	1. Myalgias responding to treatment

TABLE 6-2A

DISEASE CATEGORIES OF CASES
USED BEGINNING NOVEMBER 1996

This classification is based on involvement ever (Form 24, Items 82 A-N) and is hierarchical (e.g., pulmonary involvement is given priority over erythema nodosum).

I. Erythema Nodosum (Löfgren's Syndrome)

A constellation of signs including erythema nodosum, fever, swollen tender joints (usually ankles) and an abnormal chest X-ray. Patients need not exhibit every feature of the syndrome, but all should have erythema nodosum. (Approximately 10% of patients with erythema nodosum and sarcoidosis will have a normal chest X-ray).

II. Acute Sarcoidosis (Excluding erythema nodosum) or Chronic Sarcoidosis (Not including the fibrotic lung disease patients)

Signs of sarcoidosis without clinically manifest extrapulmonary disease.

III. Fibrotic lung disease

Patients whose chest X-rays exhibit linear streaks, small and large bullae and retraction of the hilar areas cephalad. Many of these patients manifest obstructive, as well as restrictive, dysfunction. All will have some degree of permanent lung damage resistant to current therapies.

IV. Extrapulmonary sarcoidosis

Patients whose most prominent clinical manifestations that are not pulmonary (e.g., do not have fibrotic lung disease). This group would include major acute or chronic clinically significant extra-pulmonary disease as follows:

A. Ocular - uveitis, glaucoma and/or blindness.

B. Cutaneous (excluding erythema nodosum) granulomatous skin lesions such as lupus pernio, raised erythematous nodules or plaques, or ulcerating lesions.

C. Subcutaneous nodules - palpable nodules which may range from a few millimeters to several centimeters with intact overlying skin.

D. Enlarged liver and/or significantly elevated liver blood chemistries (alkaline phosphatase > 200 IU, ALT, AST > 200 U/L) and/or evidence of portal hypertension.

E. Enlarged spleen with or without evidence of hypersplenism.

F. Neurologic - central nervous system or peripheral nerve involvement.

TABLE 6-2A (Continued)

DISEASE CATEGORIES OF CASES
USED BEGINNING NOVEMBER 1996

G. Cardiac - tachycardic or bradycardic dysrhythmias, cardiomyopathy, abnormal gallium or thallium scans.

H. Bone and Joint - clinical and radiographic evidence of bone and/or joint lesions typical of sarcoidosis.

I. Renal - hypercalcemia, nephrocalcinosis, elevated BUN and/or creatine.

Patients with extrapulmonary sarcoidosis are classified in two categories -- those with no pulmonary involvement (i.e., normal chest X-ray or Scadding category I chest X-ray); and those with pulmonary involvement (i.e., Scadding category II or III chest X-ray).

TABLE 6-2B

DISEASE CATEGORIES OF CASES
USED BEGINNING SEPTEMBER 1997

This classification counts each involvement (e.g., pulmonary involvement and erythema nodosum) independently and is based on findings at the time of the physical examination (Form 24, Items 83 A-N).

I. Erythema Nodosum (Löfgren's Syndrome)

A constellation of signs including erythema nodosum, fever, swollen tender joints (usually ankles) and an abnormal chest X-ray. Patients need not exhibit every feature of the syndrome, but all should have erythema nodosum. (Approximately 10% of patients with erythema nodosum and sarcoidosis will have a normal chest X-ray).

II. Acute Sarcoidosis or Chronic Sarcoidosis (Not including the fibrotic lung disease patients)

Signs of sarcoidosis without clinically manifest extrapulmonary disease.

III. Fibrotic lung disease

Patients whose chest X-rays exhibit linear streaks, small and large bullae and retraction of the hilar areas cephalad. Many of these patients manifest obstructive, as well as restrictive, dysfunction. All will have some degree of permanent lung damage resistant to current therapies.

IV. Extrapulmonary sarcoidosis

Patients who have prominent clinical manifestations that are not pulmonary. This group would include major acute or chronic clinically significant extrapulmonary disease as follows:

A. Ocular - uveitis, glaucoma and/or blindness.

B. Cutaneous (excluding erythema nodosum) granulomatous skin lesions such as lupus pernio, raised erythematous nodules or plaques, or ulcerating lesions.

C. Subcutaneous nodules - palpable nodules which may range from a few millimeters to several centimeters with intact overlying skin.

D. Enlarged liver and/or significantly elevated liver blood chemistries (alkaline phosphatase > 200 IU, ALT, AST > 200 U/L) and/or evidence of portal hypertension.

E. Enlarged spleen with or without evidence of hypersplenism.

F. Neurologic - central nervous system or peripheral nerve involvement.

G. Cardiac - tachycardic or bradycardic dysrhythmias, cardiomyopathy, abnormal gallium or thallium scans.

TABLE 6-2B (Continued)

DISEASE CATEGORIES OF CASES
USED BEGINNING SEPTEMBER 1997

H. Bone and Joint - clinical and radiographic evidence of bone and/or joint lesions typical of sarcoidosis.

I. Renal - hypercalcemia, nephrocalcinosis, elevated BUN and/or creatine.

Patients with extrapulmonary sarcoidosis are classified in three categories -- those with no pulmonary involvement (i.e., normal chest X-ray or Scadding category I chest X-ray); and those with pulmonary involvement (i.e., Scadding category II or III chest X-ray) or fibrosis (i.e., Scadding category IV chest X-ray).

CHAPTER 7

ORIENTATION AND CONSENT

7.1 SARCOIDOSIS PATIENT ORIENTATION

Sarcoidosis patients are informed that this is a research study intended to investigate possible causes and risk factors for sarcoidosis. They are told that the study involves collecting information and biologic samples from patients with sarcoidosis. Information is collected by questionnaire, and blood samples are collected.

Sarcoidosis patients enrolled in the study also have an evaluation performed to assess the extent and severity of their sarcoidosis. The evaluation includes a physical examination, chest X-ray, and pulmonary function testing (before and after bronchodilator administration, if clinically indicated).

Sarcoidosis patients are also informed that this study involves comparing information obtained from them with information that is obtained from control individuals who are matched to them in terms of age, gender, and race.

Sarcoidosis patients are informed that enrollment in this study does not involve alteration of their care or their treatment as determined by their usual physicians. A sarcoidosis patient is recruited for this study only if his/her usual physician(s) agree. There are no costs to the patient or to any insurance carrier for any part of the evaluation performed solely for the study and not otherwise part of usual care of patients with sarcoidosis. However, testing that is usually done as part of the care of patients with sarcoidosis is billed according to the usual method of clinical billing. For example, charges for bronchoscopy and transbronchial biopsy or lymph node biopsy and pathological examinations to establish the diagnosis of sarcoidosis remain the patient's responsibility. Patients who have erythema nodosum may be diagnosed with Kveim agent under an Investigational New Drug (IND) Application approved by the U. S. Food and Drug Administration (FDA). The use of Kveim agent requires separate orientation and consent.

The first 240 sarcoidosis patients (cases) enrolled are informed that research center staff will maintain contact by telephone or by mail at intervals of approximately six months. This contact is primarily to ensure accurate and updated information about the patient's address and telephone number. These sarcoidosis patients are informed that they are asked to return for a follow-up evaluation two years after their entry into the study. This evaluation includes an interview with completion of a questionnaire, a physical examination, a chest X-ray, blood tests, and pulmonary function tests (before and after bronchodilator administration, if clinically indicated).

Patients are informed that they will be reimbursed for their expenses to participate in the study. The amount varies among Clinical Centers and depends upon whether or not the individual has to make a special trip to the Clinical Center. Each individual receives a minimum of $25 for ACCESS-related expenses.

Bronchoscopy and transbronchial biopsy are frequently used procedures in the diagnosis of sarcoidosis. Bronchoalveolar lavage is a routine part of the procedures to obtain specimens for culture and other laboratory analysis. Residual specimens are routinely stored in freezers as part of usual clinical practice by the ACCESS Investigators. Patients with sarcoidosis who enroll in ACCESS are requested to give permission for the central storage and use for research purposes of their residual bronchoalveolar lavage specimens.

7.2 ORIENTATION OF CONTROLS

Controls are informed of the nature of the study and the method by which they were invited to participate. Potential controls are informed that random digit dialing methods are used to identify individuals with age, gender, and race matching those of a particular patient with sarcoidosis within the same telephone exchange.

Controls are informed that their participation in the study involves an interview with completion of a questionnaire and collection of a blood sample. There are no other procedures, and no follow-up is planned. Controls are informed that they will be reimbursed for their expenses to participate in the study. The amount varies among Clinical Centers and depends upon whether or not the

individual has to make a special trip to the Clinical Center. Each individual receives a minimum of $25 for ACCESS-related expenses.

7.3 INFORMED CONSENT

Written informed consent must be obtained from each case and control, and no Clinical Center may enroll cases or controls before its consent forms (approved by the Clinical Center's Institutional Review Board) are on file at the Clinical Coordinating Center. The exact language used on the Clinical Center's consent forms varies from institution to institution, but the text must be comprehensible to persons at an eighth grade reading level. No form is considered as having been given final approval until it has been reviewed by the Executive Committee.

Signed informed consent is required of each case before the case is enrolled and of each control before the control is enrolled. Specimen collection may not be performed before consent is given. The following model consent forms are included in Exhibits 7-1 (Exhibit 7-1A is the consent form for patients with sarcoidosis through September 1997 and includes Clinical Course Study follow-up. Exhibit 7-1B is the consent form in use since October 1997.) through 7-3.

7.4 AFFECTED RELATIVES

If a case or control indicates that a first degree relative (parent, sibling or child) over 18 years of age has sarcoidosis, that case or control will be asked to assist the ACCESS Investigators to obtain confirmation of the relative's diagnosis. The case or control will be provided with a letter and return postcard to send to the relative (see Exhibit 7-4). ACCESS Investigators will contact the relative only if the relative first contacts them (by telephone, return postcard or in person) to give permission for the inquires planned. Once a relative has contacted the ACCESS Investigators,

inquires will be made with the relative to determine the extent to which a diagnosis of sarcoidosis has been documented. If medical records describing sarcoidosis exist (e.g., a hospital chart with a bronchoscopy and biopsy recorded), ACCESS Investigators will request the relative's permission to obtain a copy of the appropriate records parts to document whether or not sarcoidosis was diagnosed. If a possibly affected relative does not contact the Clinical Center, the Clinical Center staff may send a letter to the enrolled case or control asking for assistance in reminding the relative of the opportunity to provide information for ACCESS (see Exhibit 7-5).

Exhibit 7-1A

CONSENT FORM FOR PATIENTS WITH SARCOIDOSIS
In Use Through September 1997

PURPOSE OF STUDY: The ACCESS Study (A Case Control Etiologic Study of Sarcoidosis) is a research project of the National Institutes of Health. Sarcoidosis is a chronic disease that often involves the lungs. The cause of sarcoidosis is unknown. This study will compare facts about patients with sarcoidosis (cases) and people without sarcoidosis (controls) to learn what causes the disease. Ten clinic research centers are in this study.

HOW CASES ARE CHOSEN: Your doctors have recently said that you have sarcoidosis. We are asking patients with newly found sarcoidosis to join this study. Your doctor has given your name to this research team. Your doctor knows that we are asking you if you want to volunteer to be part of the study.

The ten clinics will enroll a total of 720 cases for the study. Also, 720 people without sarcoidosis will enroll in the study as controls. Data and blood samples will be collected from the controls to compare with the data and blood samples from patients with sarcoidosis.

WHAT TO EXPECT: There are five parts of this study. First is an interview to record medical, environmental, and family history. Second is a physical examination by a doctor on the research team. Third, clinic staff will take a sample of your blood. Fourth, clinic staff will perform or review the results of tests that are part of usual care for sarcoidosis. Fifth, clinic staff will contact you every six months for two years and see you in the clinic two years after you join the study.

1. Interview - We will ask you detailed questions about yourself, your medical history, your family, and possible exposures. The interview will take between one and two hours. The interview will be tape recorded. The taping is being done so we can check that we have written down without errors your answers to our questions. We will erase each tape six months after we record it. Only study staff will use these tapes. You may not be able to answer all our questions at first. We may call you so you can give answers later.

2. Physical examination - A doctor on the research team will conduct a routine physical for you. This physical will not include a rectal examination. In women, the physical will not include breast or gynecologic examination (a pelvic or “internal” examination).

3. Blood sample - Study staff will take a blood sample of about three ounces (less than one-half cup) from a vein in your arm. This amount of blood is about one-fifth of the amount that is usually taken when someone donates blood. Part of this sample will be used at the present time; part will be frozen and stored for studies to be planned in the future. The portion of the blood that is frozen will be stored at a central laboratory for the National Institutes of Health. Blood samples will be handled in a manner that protects your privacy.

We will use some of the blood sample to look for gene differences that may play a part in sarcoidosis. Part of the frozen sample will be used in the future for more studies of genes. The genes we want to study may come from you or may have reached your blood from a virus, bacterium, or fungus. If you agree now, doctors in other approved studies may use the frozen samples at a later date for studies of diseases other than sarcoidosis. Your agreement or refusal to use the sample in other studies will not affect its use for current or future studies of sarcoidosis. The study will not be giving cases or controls individual results of gene tests.

Please mark the consent you give for study of your blood and the genes in your blood (check one):

9 for this sarcoidosis study only.

9 for this sarcoidosis study and for other medical research projects.

_____
Initials

Exhibit 7-1A *(Continued)*

CONSENT FORM FOR PATIENTS WITH SARCOIDOSIS
In Use Through September 1997

4. Other tests that are part of the routine care of patients with sarcoidosis - Patients with sarcoidosis usually have several other tests that are part of their care. If one of your usual doctors has done these tests, we will use the results to judge the extent and severity of your sarcoidosis. We will repeat some tests for the study, but there will be no charge to you. If one of your usual doctors has not already done these tests, we will do them as part of your routine care, and you or your insurance provider will be charged. The research team as well as your usual doctor(s) can use these results.

These tests include breathing tests, chest X-ray, and blood tests.

a. Breathing tests (pulmonary function tests) - Breathing tests are a standard method for finding out how much impact sarcoidosis has on your lungs. If not yet done, your breathing tests will be done as part of the testing that patients with sarcoidosis should have. If your own doctor has already done these tests, we will repeat them in the study center so that the breathing tests will be done in the same way for all study patients. If these are repeats of the breathing tests done by your own doctor in the last six months, there will be no charge either to you or to your insurance provider.

   As part of the breathing tests, we will give you a standard bronchodilator to inhale if they could change the results. Then part of the test will be done again. This allows us to find out whether there is any change in your breathing after treatment to open your airways. The treatment is commonly used for this purpose as part of breathing tests.

b. Chest X-ray - A chest X-ray should be part of the testing for any patient with sarcoidosis.

c. Blood tests - Several blood tests (blood cell counts, tests of liver and kidney function, and a calcium level) are usually done in patients with sarcoidosis. If your usual doctor has already done these tests, the research team will not repeat them. If they have not been done, we will perform them on some of the blood from your vein.

5. Follow-up - You will be contacted every six months for two years after you enter the study (either by phone or by mail) so that we will know about any changes in your address or phone number.

A follow-up interview, shorter than the first interview, will be done two years after your entry into the study. During this interview, study staff will ask you about your health. A chest X-ray and breathing tests will also be done as part of your care if they were not done again by your usual doctor(s). If they were done, we will repeat them in the study center to compare with your first tests here. If the testing at the study center is not part of your routine care, there will be no charge either to you or to your insurance provider.

RISKS AND DISCOMFORTS: The tests done as part of this study are all thought to be safe. There may be some discomfort from the needle used to take a blood sample. A skilled technician, nurse, or doctor will take the blood sample. There is practically no risk of infection. Only sterile, disposable materials are used. In the unlikely event that during the examinations you should require medical care, first aid will be available.

There are no physical risks from the questions. However, the interview is long. You may find that it is tiring. There are some questions about your feelings. You may find that these questions make you feel anxious for a short time.

Exhibit 7-1A *(Continued)*

CONSENT FORM FOR PATIENTS WITH SARCOIDOSIS
In Use Through September 1997

BENEFITS: There is no direct benefit to you from joining this study. We will give your doctor results of standard blood tests, breathing tests, and chest X-rays. These may be useful for the doctor taking care of you. We will tell your doctor and write a letter about anything urgent for your health care that we find.

This study may help us learn the causes and risk factors for sarcoidosis. So, there may be benefit in the future to you and to other people who have sarcoidosis now or later. We will send a brief account of the study findings to you at the end of the study.

YOUR CHOICES AND CARE: Your part in this study is purely voluntary and will not affect your care. You may refuse to join the study. You may leave the study at any time. If you do not become part of the study or if you leave it, doing so will not harm your present or future care at this hospital or clinic.

The study will not provide any treatment for your sarcoidosis. The study will not change the treatment provided by your primary doctor(s).

COST/PAYMENT: We will reimburse you $xx* to cover your expenses in the study. The study will pay for any testing for the study that is beyond the usual standard of care for sarcoidosis. Neither you nor your insurance carrier will be responsible for these costs. The research study will not pay for tests that would usually be part of your care (some listed in section 4 above) if you were not in the study. Either you or your insurance carrier is responsible for the costs of tests that are part of the standard care of patients with sarcoidosis.

No funds are in the study for you to stay overnight in the hospital. We can make no payment from the research study for testing or treatment between now and the time of the two-year follow-up. At the time of follow-up, the study will pay for any testing for the study that would not be part of the usual care of your sarcoidosis. The study will not pay for other testing that would usually be part of the care of patients with sarcoidosis.

CONFIDENTIALITY: In this study, only the research staff at the clinic where you are being studied will know your name. Facts about you that we store in the study computer will include your initials, age, gender, weight, and height. Reports from this study will not identify you personally. Your personal medical records, answers to questions, and tape recordings are private. Stored blood samples will be identified only by code numbers that cannot be traced back to you by anyone outside of the study. Study staff will not give private information to anyone outside the study except to comply with legal demands (such as a court subpoena). At the end of the study, we will make a computer tape of the study results for future use. It will not include any facts that could identify you directly. We may give facts to the National Institutes of Health, but your name will not be among those facts.

The records collected in this study will be subject to the Privacy Act. Records collected in this study can be obtained pursuant to a written request by, or with the prior consent of, the individual to whom the record pertains. The request should be made in writing to the Privacy Act Coordinator, NHLBI, NIH, Building 31, Room 5A10, 9000 Rockville Pike, Bethesda, MD 20892. Records will not be disclosed to any person or agency, unless the individual to whom the record pertains provides a written request or prior consent, except as disclosure of the record fits the criteria described in Section 3(b) of 5 U.S.C. 552a, The Privacy Act of 1974 or in the Privacy Act System Notice 0925-0126 -- Clinical Research: National Heart, Lung, and Blood Institute

*To be supplied by each Clinical Center

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Initials

Exhibit 7-1A *(Continued)*

CONSENT FORM FOR PATIENTS WITH SARCOIDOSIS
In Use Through September 1997

Epidemiological and Biometric Studies, HHS/NIH/NHLBI. In order to safeguard the records, only authorized users will have access to the records, the records will be maintained in offices that are locked when not in use, and access is strictly controlled. Robert A. Musson, Project Officer for the "A Case Control Etiologic Study of Sarcoidosis," will be responsible for monitoring contractor compliance with the Privacy Act. Except for the data tape that will not contain personal identifiers (e.g., name, social security number), contractor records pertinent to this study will be destroyed by shredding or burning within six years and three months after final payment under the contract, as described in NIH Manual Chapter 1743, Appendix 1 -- "Keeping and Destroying Records."

Exhibit 7-1A *(Continued)*

CONSENT FORM FOR PATIENTS WITH SARCOIDOSIS
In Use Through September 1997

A Case Control Etiologic Study of Sarcoidosis (ACCESS)

INFORMED CONSENT FORM

I have explained to_____, the nature and purpose of ACCESS and such risks as are involved. I have asked _____ if any questions have arisen about ACCESS and have given answers to these questions to the best of my ability.

_____

Investigator's Signature Date

I have been informed about the ACCESS study, with its possible benefits, risks and outcomes. I know that I am free to ask any questions. If I have questions about the study later, I may call (Clinical Center Principal Investigator) at (telephone number). My part in this study is voluntary. I am free to withdraw from this study at any time without impact on my care or my relationship with [name of hospital]. I may decline questions that I do not wish to answer in the course of the study.

Study doctors will use my blood sample for studies about sarcoidosis. Other doctors may use my blood samples in future studies of diseases other than sarcoidosis only if I have agreed.

I have a right to privacy. The doctors in this study will take all reasonable measures to protect the privacy of my records. My name and any other facts that might identify me will not appear in any presentation or publication from this study. My name and any other facts that might identify me will not be available to any person or group other than the investigators of this study and the Institutional Review Board of the [name of hospital], which oversees all studies.

I will receive a copy of this Consent Form. [Name of hospital] maintains an "Institutional Assurance of Compliance," a document which explains how the hospital protects people who join studies. I may have a copy of this document if I ask for one.

The [name of hospital]'s Institutional Review Board may contact me during or after this study as part of its efforts to check on people in medical studies.

In the event physical injury occurs to me, resulting from the research procedures, medical treatment will be available, if appropriate, at [name of hospital]. However, no special arrangements have been made for compensation or for payment for treatment solely because of my part in this research study.

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Initials

Exhibit 7-1A *(Continued)*

CONSENT FORM FOR PATIENTS WITH SARCOIDOSIS
In Use Through September 1997

A Case Control Etiologic Study of Sarcoidosis (ACCESS)

INFORMED CONSENT FORM
(Continued)

I agree to take part in this investigation.

I ____ do ____ do not agree to allow my blood sample to be used at a later date for studies of diseases other than sarcoidosis.

_____

Patient's Signature Date

I have witnessed the explanations made by the Investigator and heard the responses to questions.

_____

Witness's Signature Date

For any questions regarding the rights of a research participant, or information regarding treatment of research-related injuries, please contact [name of research administrator] at [telephone #].

Date submitted to Committee:_____

Exhibit 7-1B

CONSENT FORM FOR PATIENTS WITH SARCOIDOSIS
In Use Beginning October 1997

PURPOSE OF STUDY: The ACCESS Study (A Case Control Etiologic Study of Sarcoidosis) is a research project of the National Institutes of Health. Sarcoidosis is a chronic disease that often involves the lungs. The cause of sarcoidosis is unknown. This study will compare facts about patients with sarcoidosis (cases) and people without sarcoidosis (controls) to learn what causes the disease. Ten clinic research centers are in this study.

HOW CASES ARE CHOSEN: Your doctors have recently said that you have sarcoidosis. We are asking patients with newly found sarcoidosis to join this study. Your doctor has given your name to this research team. Your doctor knows that we are asking you if you want to volunteer to be part of the study.

The ten clinics will enroll a total of 720 cases for the study. Also, 720 people without sarcoidosis will enroll in the study as controls. Data and blood samples will be collected from the controls to compare with the data and blood samples from patients with sarcoidosis.

WHAT TO EXPECT: There are four parts of this study. First is an interview to record medical, environmental, and family history. Second is a physical examination by a doctor on the research team. Third, clinic staff will take a sample of your blood. Fourth, clinic staff will perform or review the results of tests that are part of usual care for sarcoidosis.

1. Interview - We will ask you detailed questions about yourself, your medical history, your family, and possible exposures. The interview will take between one and two hours. The interview will be tape recorded. The taping is being done so we can check that we have written down without errors your answers to our questions. We will erase each tape six months after we record it. Only study staff will use these tapes. You may not be able to answer all our questions at first. We may call you so you can give answers later.

2. Physical examination - A doctor on the research team will give you a routine physical examination. This physical will not include a rectal examination. In women, the physical will not include breast or gynecologic examination (a pelvic or “internal” examination).

3. Blood sample - Study staff will take a blood sample of about three ounces (less than one-half cup) from a vein in your arm. This amount of blood is about one-fifth of the amount that is usually taken when someone donates blood. Part of this sample will be used at the present time; part will be frozen and stored for studies to be planned in the future. The portion of the blood that is frozen will be stored at a central laboratory for the National Institutes of Health. Blood samples will be handled in a manner that protects your privacy.

We will use some of the blood sample to look for gene differences that may play a part in sarcoidosis. Part of the frozen sample will be used in the future for more studies of genes. The genes we want to study may come from you or may have reached your blood from a virus, bacterium, or fungus. If you agree now, doctors in other approved studies may use the frozen samples at a later date for studies of diseases other than sarcoidosis. Your agreement or refusal to use the sample in other studies will not affect its use for current or future studies of sarcoidosis. The study will not be giving cases or controls individual results of gene tests.

Please mark the consent you give for study of your blood and the genes in your blood (check one):

9 for this sarcoidosis study only.

9 for this sarcoidosis study and for other medical research projects.

_____
Initials

Exhibit 7-1B *(Continued)*

CONSENT FORM FOR PATIENTS WITH SARCOIDOSIS
In Use Beginning October 1997

4. Other tests that are part of the routine care of patients with sarcoidosis - Patients with sarcoidosis usually have several other tests that are part of their care. If one of your usual doctors has done these tests, we will use the results to judge the extent and severity of your sarcoidosis. We will repeat some tests for the study, but there will be no charge to you. If one of your usual doctors has not already done these tests, we will do them as part of your routine care, and you or your insurance provider will be charged. The research team as well as your usual doctor(s) can use these results.

These tests include breathing tests, chest X-ray, and blood tests.

a. Breathing tests (pulmonary function tests) - Breathing tests are a standard method for finding out how much impact sarcoidosis has on your lungs. If not yet done, your breathing tests will be done as part of the testing that patients with sarcoidosis should have. If your own doctor has already done these tests, we will repeat them in the study center so that the breathing tests will be done in the same way for all study patients. If these are repeats of the breathing tests done by your own doctor in the last six months, there will be no charge either to you or to your insurance provider.

   If the clinic staff think that your breathing test results may be better after inhaling a bronchodilator, they may ask you to repeat the test after the bronchodilator is administered to you. Then part of the test will be done again. This allows us to find out whether there is any change in your breathing after treatment to open your airways. The treatment is commonly used for this purpose as part of breathing tests.

b. Chest X-ray - A chest X-ray should be part of the testing for any patient with sarcoidosis.

c. Blood tests - Several blood tests (blood cell counts, tests of liver and kidney function, and a calcium level) are usually done in patients with sarcoidosis. If your usual doctor has already done these tests, the research team will not repeat them. If they have not been done, we will perform them on some of the blood from your vein.

RISKS AND DISCOMFORTS: The tests done as part of this study are all thought to be safe. There may be some discomfort from the needle used to take a blood sample. A skilled technician, nurse, or doctor will take the blood sample. There is practically no risk of infection. Only sterile, disposable materials are used. In the unlikely event that during the examinations you should require medical care, first aid will be available.

There are no physical risks from the questions. However, the interview is long. You may find that it is tiring. There are some questions about your feelings. You may find that these questions make you feel anxious for a short time.

BENEFITS: There is no direct benefit to you from joining this study. We will give your doctor results of standard blood tests, breathing tests, and chest X-rays. These may be useful for the doctor taking care of you. We will tell your doctor and write a letter about anything urgent for your health care that we find.

This study may help us learn the causes and risk factors for sarcoidosis. So, there may be benefit in the future to you and to other people who have sarcoidosis now or later. We will send a brief account of the study findings to you at the end of the study.

YOUR CHOICES AND CARE: Your part in this study is purely voluntary and will not affect your care. You may refuse to join the study. You may leave the study at any time. If you do not become part of the study or if you leave it, doing so will not harm your present or future care at this hospital or clinic.

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Initials

Exhibit 7-1B *(Continued)*

CONSENT FORM FOR PATIENTS WITH SARCOIDOSIS
In Use Beginning October 1997

The study will not provide any treatment for your sarcoidosis. The study will not change the treatment provided by your primary doctor(s).

COST/PAYMENT: We will reimburse you $xx** to cover your expenses in the study. The study will pay for any testing for the study that is beyond the usual standard of care for sarcoidosis. Neither you nor your insurance carrier will be responsible for these costs. The research study will not pay for tests that would usually be part of your care (some listed in section 4 above) if you were not in the study. Either you or your insurance carrier is responsible for the costs of tests that are part of the standard care of patients with sarcoidosis.

No funds are in the study for you to stay overnight in the hospital. We can make no payment from the research study for testing or treatment. The study will not pay for other testing that would usually be part of the care of patients with sarcoidosis.

CONFIDENTIALITY: In this study, only the research staff at the clinic where you are being studied will know your name. Facts about you that we store in the study computer will include your initials, age, gender, weight, and height. Reports from this study will not identify you personally. Your personal medical records, answers to questions, and tape recordings are private. Stored blood samples will be identified only by code numbers that cannot be traced back to you by anyone outside of the study. Study staff will not give private information to anyone outside the study except to comply with legal demands (such as a court subpoena). At the end of the study, we will make a computer tape of the study results for future use. It will not include any facts that could identify you directly. We may give facts to the National Institutes of Health, but your name will not be among those facts.

The records collected in this study will be subject to the Privacy Act. Records collected in this study can be obtained pursuant to a written request by, or with the prior consent of, the individual to whom the record pertains. The request should be made in writing to the Privacy Act Coordinator, NHLBI, NIH, Building 31, Room 5A10, 9000 Rockville Pike, Bethesda, MD 20892. Records will not be disclosed to any person or agency, unless the individual to whom the record pertains provides a written request or prior consent, except as disclosure of the record fits the criteria described in Section 3(b) of 5 U.S.C. 552a, The Privacy Act of 1974 or in the Privacy Act System Notice 0925-0126 -- Clinical Research: National Heart, Lung, and Blood Institute Epidemiological and Biometric Studies, HHS/NIH/NHLBI. In order to safeguard the records, only authorized users will have access to the records, the records will be maintained in offices that are locked when not in use, and access is strictly controlled. Robert A. Musson, Project Officer for the "A Case Control Etiologic Study of Sarcoidosis," will be responsible for monitoring contractor compliance with the Privacy Act. Except for the data tape that will not contain personal identifiers (e.g., name, social security number), contractor records pertinent to this study will be destroyed by shredding or burning within six years and three months after final payment under the contract, as described in NIH Manual Chapter 1743, Appendix 1 -- "Keeping and Destroying Records."

** To be supplied by each Clinical Center

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Initials

Exhibit 7-1B *(Continued)*

CONSENT FORM FOR PATIENTS WITH SARCOIDOSIS
In Use Beginning October 1997

A Case Control Etiologic Study of Sarcoidosis (ACCESS)

INFORMED CONSENT FORM

I have explained to_____, the nature and purpose of ACCESS and such risks as are involved. I have asked _____ if any questions have arisen about ACCESS and have given answers to these questions to the best of my ability.

_____

Investigator's Signature Date

I have been informed about the ACCESS study, with its possible benefits, risks and outcomes. I know that I am free to ask any questions. If I have questions about the study later, I may call (Clinical Center Principal Investigator) at (telephone number). My part in this study is voluntary. I am free to withdraw from this study at any time without impact on my care or my relationship with [name of hospital]. I may decline questions that I do not wish to answer in the course of the study.

Study doctors will use my blood sample for studies about sarcoidosis. Other doctors may use my blood samples in future studies of diseases other than sarcoidosis only if I have agreed.

I have a right to privacy. The doctors in this study will take all reasonable measures to protect the privacy of my records. My name and any other facts that might identify me will not appear in any presentation or publication from this study. My name and any other facts that might identify me will not be available to any person or group other than the investigators of this study and the Institutional Review Board of the [name of hospital], which oversees all studies.

I will receive a copy of this Consent Form. [Name of hospital] maintains an "Institutional Assurance of Compliance," a document which explains how the hospital protects people who join studies. I may have a copy of this document if I ask for one.

The [name of hospital]'s Institutional Review Board may contact me during or after this study as part of its efforts to check on people in medical studies.

In the event physical injury occurs to me, resulting from the research procedures, medical treatment will be available, if appropriate, at [name of hospital]. However, no special arrangements have been made for compensation or for payment for treatment solely because of my part in this research study.

_____

Initials

Exhibit 7-1B *(Continued)*

CONSENT FORM FOR PATIENTS WITH SARCOIDOSIS
In Use Beginning October 1997

A Case Control Etiologic Study of Sarcoidosis (ACCESS)

INFORMED CONSENT FORM
(Continued)

I agree to take part in this investigation.

I ____ do ____ do not agree to allow my blood sample to be used at a later date for studies of diseases other than sarcoidosis.

_____

Patient's Signature Date

I have witnessed the explanations made by the Investigator and heard the responses to questions.

_____

Witness's Signature Date

For any questions regarding the rights of a research participant, or information regarding treatment of research-related injuries, please contact [name of research administrator] at [telephone #].

Date submitted to Committee:_____

Exhibit 7-2

CONSENT FORM FOR RANDOM DIGIT DIALING CONTROLS FOR THE ACCESS STUDY

PURPOSE OF STUDY: The ACCESS Study (A Case Control Etiologic Study of Sarcoidosis) is a research project of the National Institutes of Health. Sarcoidosis is a chronic disease that often involves the lungs. The cause of sarcoidosis is unknown. This study will compare facts about patients with sarcoidosis (cases) and people without sarcoidosis (controls) to learn what causes the disease. Ten clinic research centers are in this study.

HOW CONTROLS ARE CHOSEN: We are asking you to join this study as a control because you do not have sarcoidosis. You are approximately the same age and are the same gender and race as a patient with sarcoidosis who recently joined the study. We got in touch with you by random number dialing in the same phone exchange as the patient whose age, gender and race match yours.

The ten clinics will enroll a total of 720 people without sarcoidosis in the study as controls. Also, 720 cases will enroll in the study. Data and blood samples will be collected from the controls to compare with the data and blood samples from patients with sarcoidosis.

WHAT TO EXPECT: There will be two main parts of this study. First is an interview to record facts about you. Second, clinic staff will take a sample of your blood.

1. Interview - We will ask you detailed questions about yourself, your medical history, your family, and possible exposures. The interview will take between one and two hours. The interview will be tape recorded. The taping is being done so we can check that we have written down without errors your answers to our questions. We will erase each tape six months after we record it. Only study staff will use these tapes. You may not be able to answer all our questions at first. We may call you so you can give answers later.

2. Blood sample - Study staff will take a blood sample of about three ounces (less than one-half cup) from a vein in your arm. This amount of blood is about one-fifth of the amount that is usually taken when someone donates blood. Part of this sample will be used at the present time; part will be frozen and stored for studies to be planned in the future. The portion of the blood that is frozen will be stored at a central laboratory for the National Institutes of Health. Blood samples will be handled in a manner that protects your privacy.

We will use some of the blood sample to look for gene differences that may play a part in sarcoidosis. Part of the frozen sample will be used in the future for more studies of genes. The genes we want to study may come from you or may have reached your blood from a virus, bacterium or fungus. If you agree now, doctors in other approved studies may use the frozen samples at a later date for studies of diseases other than sarcoidosis. Your agreement or refusal to use the sample in other studies will not affect its use for current or future studies of sarcoidosis. The study will not be giving cases or controls individual results of gene tests.

Please mark the consent you give for study of your blood and the genes in your blood (check one):

9 for this sarcoidosis study only.

9 for this sarcoidosis study and for other medical research projects.

_____
Initials

Exhibit 7-2 *(Continued)*

CONSENT FORM FOR RANDOM DIGIT DIALING CONTROLS FOR THE ACCESS STUDY

RISKS AND DISCOMFORTS: There may be some discomfort from the needle used to take a blood sample. A skilled technician, nurse, or doctor will take the blood sample. There is practically no risk of infection. Only sterile, disposable materials are used.
There are no physical risks from the questions. However, the interview is long. You may find that it is tiring. There are some questions about your feelings. You may find that these questions make you feel anxious for a short time.

BENEFITS: There is no direct benefit to you from joining this study. This study may help us learn the causes and risk factors for sarcoidosis. So, there may be benefit in the future to other people who have sarcoidosis now or later. We will send a brief account of the study findings to you at the end of the study.

YOUR CHOICES AND CARE: Your part in this study is purely voluntary. If you do not become part of the study, doing so will not harm your present or future care at the hospital or clinic.

COST/PAYMENT: You will be reimbursed $xx*** to cover your expenses in the study.

CONFIDENTIALITY: In this study, only the research staff at the clinic where you are being studied will know your name. Facts about you that we store in the study computer will include your initials, age, and gender. Reports from this study will not identify you personally. Your personal medical records, answers to questions, and tape recordings will be kept private. Stored blood samples will be identified only by code numbers that cannot be traced back to you by anyone outside of the study. Study staff will not give private information to anyone outside the study except to comply with legal demands (such as a court subpoena). At the end of the study, we will make a computer tape of the study results for future use. It will not include any facts that could identify you directly. We may give facts to the National Institutes of Health, but your name will not be among those facts.

The records collected in this study will be subject to the Privacy Act. Records collected in this study can be obtained pursuant to a written request by, or with the prior consent of, the individual to whom the record pertains. The request should be made in writing to the Privacy Act Coordinator, NHLBI, NIH, Building 31, Room 5A10, 9000 Rockville Pike, Bethesda, MD 20892. Records will not be disclosed to any person or agency, unless the individual to whom the record pertains provides a written request or prior consent, except as disclosure of the record fits the criteria described in Section 3(b) of 5 U.S.C. 552a, The Privacy Act of 1974 or in the Privacy Act System Notice 0925-0126 -- Clinical Research: National Heart, Lung, and Blood Institute Epidemiological and Biometric Studies, HHS/NIH/NHLBI. In order to safeguard the records, only authorized users will have access to the records, the records will be maintained in offices that are locked when not in use, and access is strictly controlled. Robert A. Musson, Project Officer for the "A Case Control Etiologic Study of Sarcoidosis," will be responsible for monitoring contractor compliance with the Privacy Act. Except for the data tape that will not contain personal identifiers (e.g., name, social security number), contractor records pertinent to this study will be destroyed by shredding or burning within six years and three months after final payment under the contract, as described in NIH Manual Chapter 1743, Appendix 1 -- "Keeping and Destroying Records."

*** To be supplied by each Clinical Center

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Initials

Exhibit 7-2 *(Continued)*

CONSENT FORM FOR RANDOM DIGIT DIALING CONTROLS FOR THE ACCESS STUDY

A Case Control Etiologic Study of Sarcoidosis (ACCESS)

INFORMED CONSENT FORM

I have explained to_____, the nature and purpose of ACCESS and such risks as are involved. I have asked _____ if any questions have arisen about ACCESS and have given answers to these questions to the best of my ability.

_____

Investigator's Signature Date

I have been informed about the ACCESS study, with its possible benefits, risks and outcomes. I know that I am free to ask any questions. If I have questions about the study later, I may call (Clinical Center Principal Investigator) at (telephone number). My part in this study is voluntary. I am free to withdraw from this study at any time without impact on my care or my relationship with [name of hospital]. I may decline questions that I do not wish to answer in the course of the study.

Study doctors will use my blood sample for studies about sarcoidosis. Other doctors may use my blood sample in future studies of diseases other than sarcoidosis only if I have agreed.

I have a right to privacy. The doctors in this study will take all reasonable measures to protect the privacy of my records. My name and any other facts that might identify me will not appear in any presentation or publication from this study. My name and any other facts that might identify me will not be available to any person or group other than the investigators of this study and the Institutional Review Board of the [name of hospital], which oversees all studies.

I will receive a copy of this Consent Form. [Name of hospital] maintains an "Institutional Assurance of Compliance," a document which explains how the hospital protects people who join studies. I may have a copy of this document if I ask for one.

The [name of hospital]'s Institutional Review Board may contact me during or after this study as part of its efforts to check on people in medical studies.

In the event physical injury occurs to me, resulting from the research procedures, medical treatment will be available, if appropriate, at [name of hospital]. However, no special arrangements have been made for compensation or for payment for treatment solely because of my part in this research study.

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Initials

Exhibit 7-2 *(Continued)*

CONSENT FORM FOR RANDOM DIGIT DIALING CONTROLS FOR THE ACCESS STUDY
A Case Control Etiologic Study of Sarcoidosis (ACCESS)

INFORMED CONSENT FORM
(Continued)

I hereby agree to take part in ACCESS.

I _____ do _____ do not agree to allow my blood sample to be used at a later date for studies of diseases other than sarcoidosis.

_____
Patient's Signature Date

I have witnessed the explanations made by the Investigator and heard the responses to questions.

_____
Witness's Signature Date

For any questions regarding the rights of a research participant, or information regarding treatment of research-related injuries, please contact [name of research administrator] at [telephone #].

Date submitted to Committee:_____

Exhibit 7-3

CONSENT FORM FOR USE OF CELLS AND FLUID RINSED FROM THE LUNGS

PURPOSE OF STUDY: The ACCESS Study (A Case Control Etiologic Study of Sarcoidosis) is a research project of the National Institutes of Health. Sarcoidosis is a chronic disease that often involves the lungs. The cause of sarcoidosis is unknown. In this study we will assess cells and fluid from the lungs of patients with sarcoidosis if the cells and fluid are saved in the course of routine diagnosis. The study doctors have planned to collect lung cells and fluid from approximately 250 of the total of 720 patients with sarcoidosis enrolled in the study. Ten clinic research centers are in this study.

HOW PATIENTS ARE CHOSEN: Patients who are going to have bronchoscopy because they may have sarcoidosis are being asked to agree to use of the bronchoscopy to collect and save the cells and fluid from their lungs. If you have questions about the bronchoscopy, you may discuss them with your doctor before agreeing to the procedure. We are asking you for your agreement to save cells and fluid now because we will not know if you have sarcoidosis until after your bronchoscopy and lab work are done. Only patients who have bronchoscopy in ACCESS hospitals are being asked to agree to saving fluid and cells for this research project.

WHAT TO EXPECT: The doctors who will do your bronchoscopy will obtain your written consent to use a bronchoscope to look into your lungs, rinse a safe fluid into and out of a portion of your lungs to obtain cells and fluid needed for your diagnosis, and to biopsy your lung tissue. The doctors in your hospital will save up to one cup of the rinsed fluid in a freezer after the amount needed has been sent to diagnostic laboratories. We are asking you to agree to allow the fluid and the cells rinsed from your lungs to be collected and saved according to the plans for ACCESS. These plans will assure that the amount of fluid collected is enough for both your diagnosis and research purposes. Making sure that enough fluid is collected will add approximately five to ten minutes to the total time for your bronchoscopy. A typical bronchoscopy lasts less than one hour.

After your diagnosis has been made, ACCESS study doctors will invite you to join this research project if you have sarcoidosis. If you join this research project, the fluid and cells being storied will be sent to the National Institutes of Health to be stored and for research tests related to sarcoidosis. Part of the frozen samples may be used at a later date for studies of diseases other than sarcoidosis. Your agreement or refusal to use the sample in other studies will not affect its use for the current study.

Please mark the consent you give for study of fluid and cells from your lungs (check one):

9 for this sarcoidosis study only.

9 for this sarcoidosis study and for other medical research projects.

If you do not have sarcoidosis, the study doctors will not return to discuss ACCESS with you. If you do not join the study (for example if you do not have sarcoidosis), you and your doctor will have the stored sample used as you and your doctor agree.

RISKS AND DISCOMFORTS: The rinse of fluid and cells from your lungs is a routine part of the diagnosis by bronchoscopy. The increase in risk of infection or reduction in oxygen level due to the procedures to make sure that enough fluid is available for diagnosis and research is small (less than 1%) although it has never been exactly measured. Up to 10% of patients may have a fever for a short time (less than one day) after the procedure.

_____
Initials

Exhibit 7-3 (*Continued*)

CONSENT FORM FOR USE OF CELLS AND FLUID RINSED FROM THE LUNGS

BENEFITS: There is no direct benefit to you from joining this study. We will tell your doctor and write a letter about anything urgent for your health care that we find.

This study may help us learn the causes and risk factors for sarcoidosis. So, there may be benefit in the future to you (if you have sarcoidosis) and to other people who have sarcoidosis now or later. We will send a brief account of the study findings to you at the end of the study.

YOUR CHOICES AND CARE: Your agreement to let us collect and save the fluid and cells rinsed from your lungs is purely voluntary and will not affect your care. You may refuse to permit this procedure and still be in the study. You may leave the study at any time. If you do not become part of ACCESS or if you leave it, doing so will not harm your present or future care at the hospital or clinic.

The study will not provide any treatment for you. The study will not change the treatment provided by your primary doctor(s).

COST/PAYMENT: There will be no cost and there will be no payment to you for the fluid and cells collected. Neither you nor your insurance carrier will be responsible for extra costs related to the fluid and cells collected for research. The study will not pay for the bronchoscopy, biopsy or obtaining fluid and cells that would usually be part of your care if you were not in the study. Either you or your insurance carrier is responsible for the cost of tests which are part of your usual care.

CONFIDENTIALITY: In this study, only the research staff at the clinic where you are being studied will know your name. Stored fluid and cells will be identified only by code number that cannot be traced back to you by anyone outside of the study. The study staff will not give private information to anyone outside the study except to comply with legal demands (such as a court subpoena). If you agree to the saving of fluid and cells that your doctor obtains during this bronchoscopy for use in the ACCESS research project, please sign this consent form.

The records collected in this study will be subject to the Privacy Act. Records collected in this study can be obtained pursuant to a written request by, or with the prior consent of, the individual to whom the record pertains. The request should be made in writing to the Privacy Act Coordinator, NHLBI, NIH, Building 31, Room 5A10, 9000 Rockville Pike, Bethesda, MD 20892. Records will not be disclosed to any person or agency, unless the individual to whom the record pertains provides a written request or prior consent, except as disclosure of the record fits the criteria described in Section 3(b) of 5 U.S.C. 552a, The Privacy Act of 1974 or in the Privacy Act System Notice 0925-0126 -- Clinical Research: National Heart, Lung, and Blood Institute Epidemiological and Biometric Studies, HHS/NIH/NHLBI. In order to safeguard the records, only authorized users will have access to the records, the records will be maintained in offices that are locked when not in use, and access is strictly controlled. Robert A. Musson, Project Officer for the “A Case Control Etiologic Study of Sarcoidosis,” will be responsible for monitoring contractor compliance with the Privacy Act. Except for the data tape that will not contain personal identifiers (e.g., name, social security number), contractor records pertinent to this study will be destroyed by shredding or burning within six years and three months after final payment under the contract, as described in NIH Manual Chapter 1743, Appendix 1 -- “Keeping and Destroying Records.”

_____
Initials

Exhibit 7-3 (*Continued*)

CONSENT FORM FOR USE OF CELLS AND FLUID RINSED FROM THE LUNGS

A Case Control Etiologic Study of Sarcoidosis (ACCESS)

INFORMED CONSENT FORM

I have explained to_____, the nature and purpose of the saving of fluid and cells rinsed from the lungs and such risks as are involved. I have asked _____ if any questions have arisen regarding the procedure and have answered these questions to the best of my ability.

_____

Investigator's Signature Date

I have been informed about the above procedure, with its possible benefits, risks and consequences. I recognize that I am free to ask any questions. If I have questions about the study, I may call (Clinical Center Principal Investigator) at (telephone number). My participation in this study is voluntary, and I am free to withdraw from this study at any time without affecting my care or my relationship with [name of hospital].

I have a right to privacy, and the investigators on this study will take all reasonable measures to protect the confidentiality of my records. My name and any other information which might identify me will not appear in any presentation or publication resulting from this study. My name and any other information which might identify me will not be available to any person or group other than the investigators of this study and the Committee on Clinical Investigation of the [name of hospital], which oversees all studies.

I will receive a copy of this Consent Form. [Name of hospital] maintains an "Institutional Assurance of Compliance," a document which explains how the hospital provides for protection of human subjects, a copy of which is available on request.

I may be contacted by the [name of hospital]'s Institutional Review Board during or after my participation in this study as part of its efforts to monitor the experience of subjects in clinical investigations.

In the event physical injury occurs to me, resulting from the research procedures, medical treatment will be available, if appropriate, at [name of hospital]. However, no special arrangements have been made for compensation or for payment for treatment solely because of my participation in this research study.

I hereby agree to participate in this investigation.

_____

Patient's Signature Date

_____

Initials

Exhibit 7-3 (*Continued*)

CONSENT FORM FOR USE OF CELLS AND FLUID RINSED FROM THE LUNGS

A Case Control Etiologic Study of Sarcoidosis (ACCESS)

INFORMED CONSENT FORM
(Continued)

I agree to my doctor's saving for research purposes up to one cup of fluid and cells rinsed from my lungs.

I _____ do _____ do not agree to allow my cells and fluid sample to be used at a later date for studies of diseases other than sarcoidosis.

_____

Patient's Signature Date

I have witnessed the explanations made by the Investigator and heard the responses to questions.

_____

Witness's Signature Date

For any questions regarding the rights of a research participant, or information regarding treatment of research-related injuries, please contact [name of research administrator] at [telephone #].

Date submitted to Committee:_____

Exhibit 7-4

LETTER TO RELATIVE TO REQUEST INFORMATION FOR ACCESS

Draft 4/3/97

Dear _____
(your relative name)

I recently participated in a study (named ACCESS) about the cause of sarcoidosis. Part of my participation involved giving a family history. I told the doctors doing the study that you were a relative who may have or may have had sarcoidosis. I did not tell them your name but I did tell them you are my _____ (enter the relationship with your relative - child, parent, brother, or sister). I am writing to ask you to give the doctors permission to collect some additional information from you over the telephone.

It is important that the doctors doing this study confirm all reported cases of sarcoidosis in my family. Your participation is voluntary and should take about five minutes. Any information they collect from you will remain confidential and will be used only for research purposes. Only if you have or had sarcoidosis will the study retain the additional information you provide. In order to insure that your confidentiality is protected, it is necessary that I send this letter, instead of the doctors contacting you directly. The doctors doing this study cannot contact you and collect important information for their study until you sign this letter and return it to them. You are not obligated to give information to the study or to reply to this letter. The researchers doing the study will appreciate any assistance you volunteer.

If you are interested in helping in this research, please:

1. Print and sign your name and enter the date below.
2. Write your address and telephone number in the space provided.
3. Circle the day and time that it is best for them to contact you.
4. Send this letter back in the enclosed self-addressed stamped envelope.

Sincerely,

_____
your name

_____
Initials

Exhibit 7-4 *(Continued)*

LETTER TO RELATIVE TO REQUEST INFORMATION FOR ACCESS

CONSENT TO CONTACT:

I agree to allow an interviewer for ACCESS to call me and ask a short questionnaire about my disease history over the phone. This information will remain confidential and only be used for research purposes.

PRINT NAME: _____

Signature: _____ Date: _____

Address: _____

_____

Telephone Number: (____ ____ ____) ____ ____ ____ - ____ ____ ____ ____

A good day and time to reach me is (please circle a day and time):

DAY: Monday Tuesday Wednesday Thursday Friday Saturday

TIME OF DAY: AM 8 9 10 11 PM 12 1 2 3 4 5 6 7 8 9

Exhibit 7-5

A Case Control Etiologic Study of Sarcoidosis (ACCESS)

AFFECTED RELATIVE REMINDER LETTER
(Sent to Case or Control)

Dear **Case/Control's Name**:

Thank you for your recent participation in A Case-Control Etiology Study of Sarcoidosis. During the review of your family history, you reported a **name type of relative** who had a history of sarcoidosis. We have not yet received the letter from your **name type of relative** indicating **his** or **her** willingness to participate in this study. It is important that the doctors doing this study confirm all reported cases of sarcoidosis in families.

As we stated before, the participation of your **name of type of relative** is voluntary, but should only take about five minutes and can be done over the phone. Any information we collect from your **name type of relative** will remain confidential and will be used for only research purposes.

We have enclosed another permission letter to give to your **name type of relative**. The doctors doing this study cannot contact your **name type of relative** until **he** or **she** signs this letter and returns it to them.

Thank you for your help and participation in this study.

Sincerely,

ACCESS Principal Investigator

CHAPTER 8

CASE AND CONTROL DATA COLLECTION

8.1 INTRODUCTION

ACCESS consists of two components: a case control study to investigate the etiology of sarcoidosis, and a prospective cohort study to investigate the clinical course of sarcoidosis. In the etiology study, sarcoidosis patients (cases) and controls are interviewed by ACCESS Clinical Center staff, asked to fill out questionnaires, and asked to provide specimens for subsequent laboratory analyses. The first 240 cases (a minimum of 20 cases from each Clinical Center) are asked to participate in the ACCESS clinical course study. In the clinical course study, Clinical Center staff contact these 240 individuals by telephone at 6, 12 and 18 months after study entry. The enrolled cases are asked to return for an examination approximately 24 months after the baseline evaluation. For cases enrolled after June 1997, the examination may be performed earlier than 24 months. Data to be collected as part of the baseline evaluation and the follow-up visits are described in this chapter.

8.2 ETIOLOGY STUDY

Sarcoidosis patients (cases) and one age-race-gender matched control for each case participate in the etiology study. This part of ACCESS requires cases and controls to complete a baseline evaluation.

Both cases and controls complete an entry evaluation for the collection of required data and biological specimens for future evaluation (see Table 8-1). The entry evaluation includes collection of demographic information (age, race, gender, residence, marital status, etc.), medical history, environmental and occupational exposure history, questions about the individual's family (first degree relatives), standardized psychosocial data on health related quality of life, and medical care usage. These data are collected by administration of ACCESS Forms (see Table 8-1).

To assist in making edit corrections to the forms, and for the purpose of quality control evaluations, the interviews in which the above information is collected are tape recorded. The tape

recording should be retained for at least six months after the interview. In addition to answering the questions in the forms, each case and control undergo phlebotomy for specific tests and for specimens to be stored in an NHLBI repository (see Chapter 10).

In addition to administration of the questionnaires, ACCESS cases have the following required procedures: physical examination, tissue biopsy, chest X-ray, spirometry (including post-bronchodialators if clinically indicated), standard biochemistry, and a complete blood count (CBC) with differential. Additional tests are performed as clinically indicated.

Table 8-1 lists the ACCESS data and specimen collection activities scheduled for the baseline evaluation for cases and controls and the 24-month follow-up evaluation for the first 240 cases.

8.3 CLINICAL COURSE STUDY

The process of recruitment for the follow-up study begins with the first case enrolled in the etiology study and continued until the end of September 1997 when 243 cases were enrolled in the Clinical Course Study. For cases agreeing to participate, a clinic visit is scheduled approximately 24 months after the patient's baseline evaluation. Cases enrolled after June 1997 may be seen in the interval 21 to 24 months after entry. The follow-up evaluation includes a medical history, physical examination, chest X-ray, spirometry, routine biochemistry, complete blood count and differential, and additional tests as clinically indicated. A follow-up blood specimen is collected. Clinical Center staff contact these ACCESS cases by telephone at 6, 12 and 18 months after entry. The telephone call is designed to maintain contact with the patient and to ask about the patient's general well being. A timeline for the Clinical Course study data collection is presented in Figure 8-1.

8.4 CLOSE-OUT PROCEDURES

ACCESS controls and the ACCESS cases not enrolled in the Clinical Course Study are closed-out of the study once all information for the entry evaluation has been collected and edited. ACCESS cases enrolled in the Clinical Course Study are closed-out after the completion of the 24-month examination. As part of the close-out procedures, cases and controls are thanked for their participation in ACCESS. They are notified that at the end of ACCESS, a brief description of the study results will be sent to them if they inform Clinical Center staff of their interest.

TABLE 8-1

ACCESS STUDY FORMS AND DATA AND SPECIMEN COLLECTION

	CASES		CONTROLS
Activity (Form)	**Baseline Evaluation**	**24-Month Follow-up**	**Baseline Evaluation**
Questionnaires 15-19	R		R
Relationship Questionnaire A (Form 20)	R		R
Relationship Questionnaire B (Form 21)	CR1		CR1
Family History Questionnaire (Form 22)	R		R
Family History Supplement (Form 23)	CR2		CR2
Physical Examination Form (Form 24)	R	R	
Laboratory Data Form (Form 25)	R	R	
Spirometry with Pre- & Post-Bronchodilators	R	R	
Complete Blood Count and Differential	R	R	
Biochemistry	R	R	
Baseline Questionnaire for Cases Only (Form 26)	R		
Follow-up Questionnaire for Cases Only (Form 27)		R	
Telephone Contact Summary (Form 28)		R*	
Chest Radiography Interpretation Form (Form 30)	R	R	
Chest X-Ray	R	R	
Diagnostic Specimen Report (Form 31)	R		
Tissue Biopsy	R		

R = Required
R* = Required at 6, 12 and 18 months after enrollment.
R+ = Required if available from clinically indicated evaluations.
R++ = Required if initial diagnosis of sarcoidosis is probable or possible.
CR1 = Required if participant has biological children.
CR2 = Required if participant has more than nine siblings.

TABLE 8-1 (Continued)

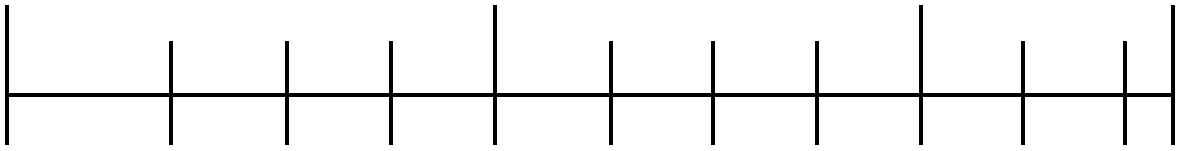
ACCESS STUDY FORMS AND DATA AND SPECIMEN COLLECTION

Activity (Form)	CASES		CONTROLS
	Baseline Evaluation	24-Month Follow-up	Baseline Evaluation
Bronchoalveolar Lavage (BAL) Form (Form 32)	R+		
Tissue Sample Shipping form (Form 40)	R++		

R = Required
R* = Required at 6, 12 and 18 months after enrollment.
R+ = Required if available from clinically indicated evaluations.
R++ = Required if initial diagnosis of sarcoidosis is probable or possible.
CR1 = Required if participant has biological children.
CR2 = Required if participant has more than nine siblings.

FIGURE 8-1

CLINICAL COURSE STUDY:
SCHEDULE FOR SARCOIDOSIS CASE ASSESSMENT (IN MONTHS)*



0 months	3	6	9	12	15	18	21	24	27	30
1a		1b		1b		1b		1c		
2								2		
3								3		
4								4		
5								5		
6								6		
7										

1a) Entry evaluation (questionnaires)
1b) Telephone contact
1c) Follow-up questionnaire
2) Medical history and physical examination
3) Chest X-ray (posteroanterior view only)
4) Spirometry (Pre- and Post-Bronchodilator)
5) Laboratory: Biochemistry, complete blood count
6) Optional: Testing of other organs as indicated by clinical symptoms/signs
7) Biological specimen collection (see Chapter 10).

* The following intervals are used to bracket data collection for each time period: ± 1 month for entry evaluation and for telephone contacts scheduled at 6, 12 and 18 months. For the 24-month follow-up visit, the interval for data collection may extend to 30 months after enrollment, but should be as close to 24 months from enrollment as possible and should not be less than 21 months from enrollment. Data obtained outside of these windows are to be collected, although centers will emphasize the need to maintain maximum data collection within the bracketed windows.

CHAPTER 9

CLINICAL COURSE

9.1 INTRODUCTION

The objectives of this part of ACCESS are: (1) to distinguish sarcoidosis patients who do and do not clinically resolve over a two-year period of follow-up, and (2) to develop a clinical/radiological/physiological sarcoidosis assessment system for reporting the severity of disease.

We will examine the relationship between the change in disease status and genetics, environment, habits, access to medical care, compliance with medical management, occupation, psychosocial variables, and socioeconomic status as described in Chapter 3.

9.2 SCHEDULE OF EVALUATIONS

Study patients with sarcoidosis (cases) enrolled within the first year of the study -- the first 240 cases -- are to be contacted and evaluated at the following time intervals (Figure 9-1):

A. Telephone Contact: every six months, for purpose of patient tracking and retention.

B. Clinical reassessment: 24 months.

Cases eligible for longitudinal follow-up (the first 243 cases) were enrolled by the end of September 1997, and all clinical reassessments will be completed by June 1999. The 24-month evaluation is performed as close to 24 months from enrollment as possible in an interval that may extend to 30 months from enrollment and does not begin less than 21 months from enrollment. Cases' baseline data are not excluded from cross sectional analyses if the 24-month follow-up visit is missed.

9.3 STUDY POPULATION

Case accrual and distribution of cases is in accordance with the procedures for examining sarcoidosis etiology as described in Chapter 6.

All patients with sarcoidosis enrolled in ACCESS within the interval described in Section 9.2 are eligible for the Clinical Course Study. Patients are not excluded from consideration if they are receiving corticosteroids or other immunomodulatory medications.

9.4 CLINICAL OUTCOME MEASURES

We are categorizing cases according to disease severity and change over time in two ways: (1) using a clinical assessment system and (2) by examining change in specific question responses, physical examination, and physiological and radiological parameters (e.g., FVC % predicted). The tests and instruments administered at time of enrollment and at the 24-month visit, are described in Sections 9.4.1 - 9.4.6.

9.4.1 Symptom Reporting

The questionnaire administered at entry and follow-up includes: identical questions aimed at characterizing clinical symptoms. In addition, the follow-up questionnaire includes questions needed to test hypotheses concerning the association between disease resolution/progression and (a) medication use, (b) socioeconomic status, (c) access to care, and (d) environmental changes (e.g., smoking, job, residence).

9.4.2 Physical Examination

The clinical examination is used to identify evidence of sarcoidosis disease resolution or progression, e.g., change in existing signs or development of new organ involvement. A standardized physical examination form is used at all centers to record the presence, absence, and extent of physical examination findings pertinent to the clinical course of sarcoidosis. This form includes a checklist of organ systems involved and a checklist of data relied upon in determining that an organ system is involved. Each center has designated investigators who perform these examinations and record results. The physical examination includes: vital signs, respiratory tract (including nasosinus), skin, lymph nodes, glands, cardiac, eyes, abdominal (liver, spleen), and nervous system.

9.4.3 Chest Radiograph (Posteroanterior)

A posteroanterior (PA) chest radiograph is obtained for clinical use on each sarcoidosis patient at the times designated in Figure 9-1. Chest X-ray readings are the responsibility of Clinical Center staff (e.g., the Clinical Center Principal Investigator) .

9.4.4 Spirometry

Simple spirometry is a valid, reproducible means of monitoring for change in the severity of the respiratory component in sarcoidosis. Spirometry is performed in a standardized manner in accordance with American Thoracic Society (ATS) guidelines, as described in the ACCESS Spirometry section of Chapter 3 in the ACCESS Procedures Manual Volume I.

9.4.5 Laboratory Tests (Blood)

The laboratory tests listed below provide important information for assessing the presence of organ involvement (e.g., liver, renal, hematopoietic). The following tests are performed following the schedule in Figure 9-1: biochemistry including total protein, albumin, alkaline phosphatase, aspartamine aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, serum urea nitrogen, creatinine, and calcium; and complete blood count (CBC) including hemoglobin, hematocrit, platelet count, and white blood cell count with differential. Laboratory data collected by referring physicians (not as a direct result of this study) are accepted in lieu of study testing if standard laboratory methods have been used and sampling occurred within the data collection windows specified in Figure 9-1.

9.4.6 Follow-up Testing of Other Organs

Additional testing and evaluation of other organs are performed at the initial and 24-month time points based on clinical signs or symptoms. Not all patients require all tests. Administration of tests is guided strictly by clinical judgment and by the nature of the abnormalities detected in these organs at the time of initial evaluation or at interval evaluations, as problems arise. Thus, certain interim data may be collected and potentially utilized even though these data were <u>not</u> systematically collected in all subjects such as slit lamp examinations of the eyes, echo-

cardiography, etc. A checklist developed as part of the Physical Exam Form is be used to track what special tests were done to examine these other organ systems, facilitating future ancillary studies.

9.5 SARCOIDOSIS ASSESSMENT SYSTEM

One of the goals of this study is the application of a clinically useful sarcoidosis assessment system (SAS), based on clinical symptoms, radiographs, physiology, and physical findings. The SAS is also used to categorize study cases who have or have not clinically resolved in two years based on respiratory and non-respiratory organ involvement (see Table 9-1).

9.6 PATIENT RETENTION

To assure return for the required 24-month follow-up visit, efforts will be made to promote a sense of group participation in an important endeavor. Such efforts will include (1) a description of this important multicenter NIH study to be provided to participants at time of entrance into the study, and (2) a card of appreciation for continued participation sent on each anniversary of enrollment. Clinical Center staff make telephone calls and mail reminder post-cards to the patient's home approximately two weeks prior to the date of the visit. All treating physicians are kept apprised of patient participation and of results.

Patients are contacted by telephone to keep current on their most recent addresses and major changes in clinical status (recent hospitalizations or unexpected medical visits) between the two visits. The emphasis is on tracking of patients, not on data collection.

9.7 STANDARDIZATION OF TREATMENT

Treatment guidelines are based on conservative therapy for patients who are asymptomatic or have mild clinical abnormalities and steroid therapy for patients whose symptoms and abnormalities indicate therapy. These guidelines are applied in all Clinical Centers to the extent feasible for a referral patient population. It is anticipated that these guidelines will reduce variability among Clinical Centers in the assessment of clinical course.

9.8 ANTICIPATED CLINICAL COURSE FINDINGS AND LIMITATIONS

Because some forms of sarcoidosis are slowly progressive and others are highly variable in their progression, a 24-month follow-up period may provide only limited insight into the clinical course of this disorder, especially as it relates to end stage disease measured with insensitive clinical tools. Although lack of central control of treatment plans limits the interpretation of study data, the therapeutic guidelines may be useful to standardize treatment so that comparisons of outcome according to patient characteristics are more clear than they would be without guidelines (see Section 9.7).

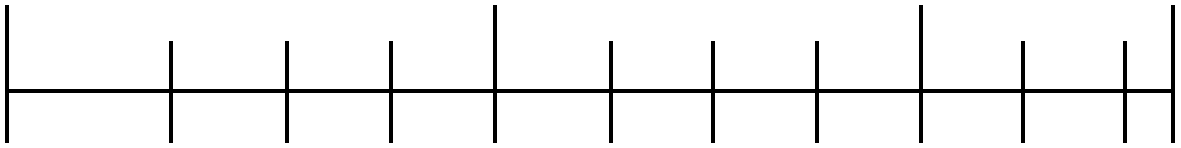
The goals of this study are to increase our understanding of the clinical course of sarcoidosis in several important regards.

1. It will clarify the relationship of age, race, gender, geography, climate, home environment, work environment, lifestyle, socioeconomic, access to medical care, and other such variables on the clinical course of sarcoidosis. The likely findings will be that one or more of these variables are associated with persistence or with spontaneous resolution of disease or with more favorable response to treatment.
2. It will permit us to examine not only sarcoidosis as a single disease but to stratify it based on clinical presentation (e.g., acute versus chronic), thereby identifying specific individual and combined risk factors for disease progression. A likely outcome will be the identification of sarcoidosis subgroup-specific risk factors for progression.
3. It will lead to a better understanding of the use of baseline evaluations of chest roentgenograms, biochemistry measurements, hematology measurements, clinical evaluations and other biological markers in predicting change over time. A likely outcome will be the recognition of what factors are associated with different clinical outcomes of sarcoidosis patients.
4. It will lead to the development and piloting of a sarcoidosis assessment system (SAS) of potential utility in assessing disease severity, progression and therapeutic response.

FIGURE 9-1

CLINICAL COURSE STUDY:

SCHEDULE FOR SARCOIDOSIS CASE ASSESSMENT (IN MONTHS)*



0 months	3	6	9	12	15	18	21	24	27	30
1a		1b		1b		1b		1c		
2								2		
3								3		
4								4		
5								5		
6								6		
7										

1a) Entry evaluation (questionnaire)
1b) Telephone contact
1c) Follow-up questionnaire
2) Medical history and physical examination
3) Chest X-ray (posteroanterior view only)
4) Spirometry (post-bronchodilator if clinically indicated)
5) Laboratory: Biochemistry, complete blood count
6) Optional: Testing of other organs as indicated by clinical symptoms/signs
7) Biological specimen collection (see Chapter 10).

* The following intervals will be used to bracket data collection for each time period: ± 1 month for entry evaluation and for telephone contacts scheduled at 6, 12 and 18 months. For the 24-month follow-up visit, the interval for data collection may extend to 30 months after enrollment, but should be as close to 24 months from enrollment as possible and should not be less than 21 months from enrollment. Data obtained outside of these windows are to be collected, although centers will emphasize the need to maintain maximum data collection within the bracketed windows.

Table 9-1

Sarcoidosis Assessment System

PURPOSE

The purpose of the sarcoidosis assessment system (SAS) is to establish an instrument to describe the clinical state of sarcoidosis patients. The SAS should identify patients whose sarcoidosis is worsening, improving or is inactive.

GENERAL DESCRIPTION

The SAS has two axes:

A. A pulmonary severity component which is a composite clinical-radiographic-physiologic score (CRP-S) modeled after a similar score developed for idiopathic pulmonary fibrosis (Watters et al, 1986).

The CRP-S rating system involves three separate evaluations:

1. A clinical rating, which is a dyspnea scale.
2. A radiological rating composed of the presence of specific radiological findings.
3. A physiologic rating composed of pulmonary function tests.

B. An extrapulmonary organ rating:

The extrapulmonary organ rating involves two evaluations:

1. Degree of evidence of organ involvement: definite, probable, possible or none.
2. Severity of organ involvement.

VALIDATION

Since most data collected to compute the SAS are used by clinicians to determine the clinical state of sarcoidosis patients, validation of the SAS may be biased. As a crude validation technique, SAS scores could be computed retrospectively on sarcoidosis patients who have (1) required no therapy for more than one year or (2) have died.

Table 9-1 (Continued)

Sarcoidosis Assessment System

CLINICAL ASSESSMENT

Level of Dyspnea

Not troubled with breathlessness except with strenuous exercise

Troubled by shortness of breath when hurrying on the level or walking up a slight hill

Walks slower than people of the same age on the level because of breathlessness or has to stop for breath when walking at own pace on the level

Stops for breath after walking about 100 yards or after a few minutes on the level

Too breathless to leave the house or breathless when dressing or undressing

RADIOLOGICAL ASSESSMENT

Radiological Findings

Hilar or mediastinal adenopathy

Hilar retraction

Alveolar infiltrates

Pulmonary hypertension

Interstitial disease

Stage 4 disease

Bullae, blebs or cysts

PHYSIOLOGICAL ASSESSMENT

Spirometry

FVC (% Predicted)
FEV_1/FVC (%)

EXTRAPULMONARY ORGAN ASSESSMENT

Table 9-1 (Continued)

Sarcoidosis Assessment System

Each organ is rated separately as not clinically involved, clinically involved but functioning, and failed (including death related to organ involvement).

Extrapulmonary organs include:

Bone/Joints
Ear/Nose/Throat
Renal (not nephrolithiasis)
Parotid/Salivary glands
Muscles
Skin
Eyes
Neurologic
Hypercalcemia, hypercalcuria, or nephrolithiasis
Spleen
Cardiac
Liver
Non-Thoracic lymph node
Bone marrow

Organ failure is defined as follows:

1. Death related to failure of the organ
2. Liver, heart, kidney: organ transplantation
3. Kidney: dialysis required
4. Eye: blindness

EVIDENCE OF INVOLVEMENT

Determined using the criteria in Table 6-1 of the protocol:

Definite
Probable
Possible
No involvement

Table 9-1 (Continued)

Sarcoidosis Assessment System

Assessments are made at study entry and two years. The two-year SAS is compared to the entry SAS to make assessments.

Significant change in components of the pulmonary data set are:

Radiographic Rating: Development or resolution of at least one radiographic finding listed in the radiographic rating

Clinical Rating: $ 1 level change in dyspnea

FVC: $ 15% change from last assessment

FEV_1/FVC: $ 5% change from last assessment

Normal pulmonary assessment is defined as the lowest level on the dyspnea scale, no abnormal radiographic findings on the radiographic rating, and normal spirometry.

Improving pulmonary assessment is defined as improvement of at least two of the four pulmonary assessment data set measures (clinical rating, radiographic rating, FVC, FEV_1/FVC, D_LCO), with no improvement of any pulmonary assessment data set measure.

Normal extrapulmonary assessment is no extrapulmonary organ involvement. If an organ has been previously involved, it is considered no longer involved if there are no positive responses concerning that organ on evaluation in ACCESS (positive historical responses that relate to time prior to the last assessment are NOT considered positive responses).

Worsening extrapulmonary assessment is development of new organ involvement or change in severity of organ involvement.

Improving extrapulmonary organ involvement is resolution of involvement of at least one organ with no new organ involvement.

Treatment is defined as:

The use of oral or intravenous corticosteroids, methotrexate, azathioprine, cyclosporine, and/or another immunosuppressive medication at any dose.

Treatment does NOT include topical immunosuppressive medications such as inhaled corticosteroids. It also does NOT include medications used for control of symptoms such as inhaled beta agonists or nonsteroidal anti-inflammatory agents.

Table 9-1 (Continued)

Sarcoidosis Assessment System

Five clinical states are defined:

1. Resolution
Normal pulmonary and extrapulmonary assessment while not on treatment for at least one year (since prior to the last assessment).

2. Improvement
Improvement in pulmonary or extrapulmonary assessment with no worsening of the other.

3. Worsening
Worsening in pulmonary or extrapulmonary assessment with no improvement of the other.

4. Unchanged
No worsening or improvement in assessment (either 2 or 3 as defined above) while not on treatment for at least one year (since prior to the last assessment).

5A. Status indeterminant, on treatment
On treatment or off treatment less than one year and does not satisfy clinical states 2 (improvement) or 3 (worsening) above.

5B. Status indeterminant, off treatment
Off treatment for at least one year with improvement in one assessment (pulmonary or extrapulmonary) with worsening of the other assessment.

CHAPTER 10

BIOLOGICAL SPECIMENS

10.1 OVERVIEW

The purpose of this chapter is to provide guidelines for the collection and disposition of biological specimens (blood and bronchoalveolar lavage cells and fluid) in ACCESS. Broncho-alveolar lavage (BAL) specimens are collected as residual specimens from clinically indicated bronchoscopy procedures.

A summary of blood samples required from cases and controls in ACCESS follows:

Whole blood:	54 ml	in EDTA	
	40 ml	in heparin	only for those Clinical Centers providing cell pellets for RNA analysis by differential display polymerase chain reaction (DD-PCR) as part of the special laboratory study at the Beth Israel Deaconess Medical Center; unless specifically notified by the Executive Committee ACCESS Clinical Centers other than the Beth Israel Deaconess Medical Center do not collect these specimens.

Study forms and data files are used to track processing, shipment and receipt of biological specimens used in ACCESS from Clinical Centers to Core Laboratories, Special Study Laboratories and the Central Repository (see Chapter 6 of ACCESS Procedures Manual, Volume I for details). All specimens collected and shipped including (blood and bronchoalveolar lavage) must be handled according to universal precautions including double-bagging of mailed specimens. If a specimen is known to be infectious, it must be shipped following the additional procedures outlined in the ACCESS Procedures Manual Volume I, Chapter 6.

10.2 BLOOD SAMPLE COLLECTION

10.2.1 Phlebotomy

Phlebotomy should be performed by venipuncture using a large enough needle (size #19 or lower) to avoid hemolysis and trauma whenever possible, and limited use of the tourniquet. Polyvinylpropyleneiodine (PVP) must be used to clean the subject's skin and the rubber stopper of the vacutainer tube.

Sterile vacutainers should be used. The vacutainer tubes to use are: five large (10 cc) purple top (EDTA), four large (10 cc) green top (heparin [selected Clinical Centers only]) and one small (4 cc) purple top (EDTA) tubes. The small (4 cc) purple top (EDTA) tube should be collected first.

Phlebotomy should be timed so that specimens can be received at the core facilities (see below) between Tuesday and Friday. Clinical Center staff should send e-mail notification to core facilities the same day shipments are sent to assist core facility staff preparation for specimen receipt. By special arrangement the DNA Core Laboratory and Special Study Laboratory for Mycobacterial Cell Wall Deficient Forms will receive specimens on Saturday; Clinical Center investigators must contact the Directors of the appropriate Laboratories before noon on Friday to determine whether or not a specimen can be received on Saturday.

10.2.2 Processing Blood Samples

All five large (10 cc) purple top tubes should be labeled and shipped by overnight mail at ambient temperature to the DNA Core Laboratory for processing of samples for DNA and plasma.

One small (4 cc) purple top tube should be labeled and shipped to the Specialized Study Laboratory for Mycobacterial Cell Wall Deficient Forms by overnight mail at ambient temperature for special cultures.

Initially only the Beth Israel Deaconess Medical Center patients provide specimens for the DD-PCR special laboratory study. For Clinical Centers providing blood cells for RNA analysis all

four large green top tubes should be used to isolate peripheral blood mononuclear cells (PBMC) using a standard ficoll-hypaque separation technique. The PBMC should be centrifuged into a cell pellet, resuspended in solution D (guanidimium based solution) and stored at -70^{o}C; shipping of these samples on dry ice should occur within one month to the DD-PCR Special Laboratory for ACCESS.

PBMC are prepared in the local Clinical Center as outlined in the Procedures Manual Volume IV for the Special Study Laboratory for Defining Etiologic Sarcoid Antigen in Kveim Reagent.

10.3 KVEIM BIOPSIES

Tissue diagnosis may be established with a Kveim skin test biopsy for patients who have Löfgren's syndrome (as defined by erythema nodosum). The use of the Kveim skin test in ACCESS is permitted under an Investigational New Drug (IND) Application approved for Dr. Alvin Teirstein by the U.S. Food and Drug Administration (FDA). All physicians using the Kveim skin test in ACCESS must adhere to the procedures described in Dr. Teirstein's IND proposal, obtain the patient's informed consent for use of Kveim and report adverse reactions. Tissue specimens may be sent to Dr. Teirstein for all histopathology processing.

For patients whose diagnosis is made locally with Kveim biopsy tissue confirmation, one pathology slide stained with hematoxylin and eosin should be sent to Dr. Teirstein at Mount Sinai Medical Center (see Chapter 6 of ACCESS Procedures Manual Volume I).

10.4 BRONCHOALVEOLAR LAVAGE (BAL) SPECIMENS

The recommended systematic approach to the collection, handling, and interpretation of bronchoalveolar lavage cells and fluid for patients in ACCESS is based on the collective experience of the groups involved. Final details of the techniques have been developed as the result of a questionnaire that established that each Clinical Center uses BAL techniques that are sufficiently comparable to allow for standardized specimen collection. Patient samples are

routinely cultured in Clinical Centers for mycobacteria and fungi. Either bronchial wash or BAL samples may be sent for culture. It is not required that both be sent unless it is the standard procedure of that institution. Sampling for cytology and bacterial cultures is done only if clinically indicated. Residual BAL specimens available following clinically indicated bronchoscopy procedures are stored in ACCESS Clinical Centers at -80^{o} C and transported, frozen to the Central Repository operated by McKesson Bioservices under contract with the NHLBI.

Standardized procedures recommended for BAL are:

1. BAL should be performed in the areas of the middle lobe or lingula in patients with diffuse disease and in the area of most disease in those patients with local disease.
2. The lavage volume should be 240 ml.
3. The fluid should be collected either by hand-held syringe or low-pressure suction.
4. For the purpose of the study, only one area should be analyzed and collected.
5. The gauze technique should not be used.
6. The initial 20 ml aliquots should not be discarded, but be part of the preparation.
7. From the cell count, determine the amount or dilution of neat fluid to use. The concentration should be about 0.2 x 10^6 cells/ml. The following are some rough pre-determined dilutions:

   $\leq$ 30 x 10^5 cells, use 200 µl neat fluid;

   30-59 x 10^5 cells, use 100 µl neat fluid;

   $\geq$ 60-149 x 10^5 cells, use 1:2 dilution, 100 µl neat fluid and 100 µl Roswell Park Memorial Institute (RPMI) solution or normal saline;

   > 150 x 10^5 cells, use 1:3 dilution, 100 µl neat fluid and 200 µl RPMI solution or normal saline.
8. Unstained slides and Wright-Giemsa stained slides are made available to the BAL Core Laboratory for cell counts.
9. Cell counts as well as lymphocyte subpopulations using flow activated cell sorting are performed at the local laboratory. Additional markers beyond those to determine

general T cell population, including CD4 and CD8 subpopulations, may be used, as clinically indicated.

10. In addition to the stained and unstained slides, BAL samples are also held for aliquots for shipment to the Central Repository. In particular, four 2 ml aliquots are held at -80^{o} C, and the cell button is prepared and stored at -80^{o} C for shipment to the Central Repository.

Each center prepares three sets of slides (six slides in three pairs of one Wright-Giemsa stained slide and one air dried slide). One set is kept at the Clinical Center; one set is sent to the Central Repository; and one set is sent for differential cell counts in the BAL Core Laboratory. Pairs of BAL slides for differential cell count in the BAL Core Laboratory are labeled and stored in the Clinical Center for shipment within four to six weeks. Each shipment to the BAL Core Laboratory should be accompanied by the ACCESS Bronchoalveolar Slide Transmittal List (Form 65). Pairs of slides should be sent in standard slide transport packaging (e.g., cardboard slide holders) labeled with each patient's ACCESS specimen number label, secured for transport (i.e., so that slides will not fall out of holders), and packed appropriately (i.e., well protected in an envelope or package marked fragile).

Batches of pairs of slides should be sent to the BAL Core Laboratory and Central Repository. If only one pair of slides is available for a case, send the slides to the BAL Core Laboratory with a note indicating that these are the only slides available and should be sent from the BAL Core Laboratory to the Central Repository (with a properly completed transmittal form) after review in the BAL Core Laboratory.

BAL specimens are stored, frozen at the Clinical Center ready for shipment to the Central Repository within four to six weeks. Each shipment to the Central Repository should be accompanied by the ACCESS Bronchoalveolar Lavage Transmittal List (Form 60). Shipping materials are provided by the Central Repository.

CHAPTER 11

DISTRIBUTED DATA SYSTEM

11.1 OVERVIEW

The ACCESS distributed data management system was designed and implemented by the Clinical Coordinating Center staff. The system allows Clinical Center staff to enter data from case and control study forms and to transmit the data to the Clinical Coordinating Center. The system provides other functions including an inventory of all forms entered. Clinical Center staff have responsibility for maintaining the integrity of the local database by performing regular back-ups. The Clinical Center staff are responsible for the security of the distributed data management system hardware.

Clinical Center staff use an automated telephone response system (ATRS) to register cases. This system is also used to monitor the Clinical Center progress in the enrollment of potential controls identified by random digit dialing (RDD).

A manual (ACCESS Procedures Manual, Volume III) describing the procedures for using the ACCESS data management system was provided by the Clinical Coordinating Center to each Clinical Center.

11.2 DATA ENTRY

The data entry function provided uses screen images of forms. Data are edited for valid codes and ranges during data entry. A local edit, which includes a check of consistency of data within the form, is performed after data entry. Messages are printed locally. A more extensive edit is performed after the data are transmitted to the Clinical Coordinating Center. Clinical Center staff are able to correct items using a screen image of the data form. A record of each change is stored in the database. As forms are entered or corrected, they are marked for transmission to the Clinical Coordinating Center.

Each staff member certified by the Clinical Coordinating Center to perform data entry is assigned a data entry certification number. Paper copies of a sample of forms are requested by the Clinical Coordinating Center at regular intervals to assess the quality of data entry.

11.3 DATA TRANSMISSION

Data are transmitted to the Clinical Coordinating Center on a regular schedule. Once every week, Clinical Coordinating Center staff link with the computer at each Clinical Center for transmission of data entered in the previous week. At that time, Clinical Coordinating Center staff may also transmit study reports or new software for use in the Clinical Center.

11.4 OTHER FUNCTIONS

Screening logs for cases and potential controls identified by the RDD Interview Group to match enrolled cases include a limited amount of information (see Section 6.2) concerning each potential case and control identified. Completion of screening logs for cases was discontinued in October 1997. These logs are entered and updated locally using the distributed data management system.

Data entry certification is completed by entering a standard set of forms into the local database. These data are sent to the Clinical Coordinating center during regularly scheduled transmissions.

Local reports include case appointment schedules for cases enrolled in the Clinical Course Study, visits expected in a calendar month for these cases, delinquent forms for cases and controls, and calculation of reference dates for controls (implemented July, 1997).

Software to assist in scheduling case and control appointments is also available.

11.5 DATABASE BACKUP

The Clinical Coordinating Center database is the archive for all data from the Clinical Centers. Each individual Clinical Center must protect its own computer system from loss of study data. Software is provided for backup of the database as well as for backup of the

system. The ACCESS database is backed up after each data entry session. The system is backed up at regular intervals. A recommended procedure for system backup is to copy all files once each week and to copy only changed files daily.

11.6 REQUIREMENTS

The hardware for the distributed data management system requires a secure workspace with a power source (preferably protected from surges and interruptions) and a dedicated telephone line. Space to store paper and labels should be available. A touch-tone phone is required to use the automated telephone response system (ATRS).

11.7 CASE AND CONTROL REGISTRATION

Cases are registered using an automated telephone response system (ATRS). Clinical Center staff complete a worksheet with identifying information and eligibility information. Clinical Center staff call the ATRS and enter the worksheet data using a touch-tone telephone. Using the case registration data, potential controls are identified through random digit dialing. After the potential control has been contacted, Clinical Center staff update the potential control's status in ACCESS using the ATRS.

11.8 ELECTRONIC DOCUMENTS (IMPLEMENTED MAY 1998)

The ACCESS Protocol and Procedures Manuals are available in electronic form on ACCESS microcomputers. Revised documents are downloaded during data transmission (Section 11.3).

CHAPTER 12

STATISTICAL CONSIDERATIONS

12.1 INTRODUCTION

Data analyses will be carried out for two main purposes. One is to monitor the performance of the Clinical Centers with respect to recruitment of cases and controls, follow-up of cases, adherence to the study protocol, and accuracy and completeness of study data. The second main purpose for data analyses is to seek answers to the study research questions and objectives. These analyses will involve the application of case control and longitudinal data analysis methods. Interim research data reports will be generated every six months and presented to the Data and Safety Monitoring Board. A final report will be generated at the termination of recruitment and follow-up of the cases.

The analyses proposed for A Case Control Etiologic Study of Sarcoidosis (ACCESS) are robust from the point of view that they will allow for multivariate analyses, missing data and different lengths of follow-up of the cases.

There are two types of analyses in ACCESS. First, a case control study will be conducted with one matched control for each case (case control pairs). Second, the first 240 cases enrolled in ACCESS will be followed for two years.

For the case control study, controls will be matched to cases on the basis of age (± 5 years), gender and race: the control will be identified using random digit dialing methods. The final statistical design of the case control study will have adequate control mechanisms for bias and confounding and the design will allow for the detection of important associations. Most important will be the rigid matching of race in the paired design. Among the hypotheses being tested are the effect of modifications of certain exposures among patients with a genetic predisposition for sarcoidosis. Certain alleles are not common to both black and white comparisons. Therefore, it will be important to match for race in these analyses. Evaluations of the adequacy of the number

of cases and controls and of the power of the major proposed comparisons are important aspects of establishing if meaningful associations of exposure variables with cases can be measured.

Assessments of the number of cases in the longitudinal analysis must take account of the different types of outcome data that will be collected, as well as the data collection techniques for independent and dependent variables.

Five categories of sarcoidosis cases will be recruited, and progression or regression of the disease may be different according to the different categories. Therefore, it is anticipated that subgroup analyses will be part of ACCESS.

In the clinical course study, synthetic case control methods will be used to analyze data obtained from specimens stored in the Central Repository. This design will produce a substantial cost savings over the standard designs that require routine analyses for all samples collected, and has the added advantage that certain assays may not be developed at this time, but could be performed later on banked specimens.

12.2 POWER CALCULATIONS

12.2.1 Power Calculations for the Case Control Study

Determination of power for matched pair designs have been developed by Miettinen (Miettinen, 1969) and Walter (Walter, 1980) and more recently by Lubin, Gail, and Ershow (Lubin et al, 1988). These formulas can be used to evaluate the adequacy of the number of cases and controls in the case control design.

For binary exposure variables analyzed as part of the case control study the formula for power is the following:

$$\text{power} = \Phi\left(\frac{\Delta\sqrt{k\,N}}{\sqrt{\phi(k+1)/2}} - Z_{\alpha}\right),$$

where Z_{α} would be 1.96 (α = 0.05 two sided test), N is the number of cases, k is the number of controls matched to each case (k = 1 in ACCESS), Δ is the difference between the expected percentages of cases and controls exposed to the risk factor of interest (p_1 - p_0) and ϕ is the

proportion of case control pairs in which one person's exposure history differs from the other (discordance). Breslow and Day (Breslow and Day, 1980) have shown that only the discordant pairs in a case control study contribute information to the estimation of the odds ratio. Thus, discordant pairs are "informative".

Matched case control study analysis differs from prospective study or clinical trials data analysis. Psi (ø) is dependent upon the degree of correlation between the probability that a case is exposed (has an attribute) and the probability that the control for this case is exposed. This correlation will be a function of the values of the matching covariates and thus the probabilities of exposure will vary from pair to pair and a correlation between these probabilities will be present.

Let p_1 be the expected percentage of exposure in the cases,

p_0 be the expected percentage of exposure in the control,

and $Cov(p_1,p_0)$ be the expected covariance of the matched case and control exposure probabilities.

then $\phi = p_1 + p_0 - 2\,p_1\,p_0 - 2\,\mathrm{cov}\,(p_1, p_0)$.

This can be rewritten to:

$$\phi = \frac{1-\Delta^2}{2} - 2(\bar{p}-0.5)^2 - 2\mathrm{cov}\,(p_1, p_0) \quad ,$$

$$\text{with } \bar{p} = \frac{p_1+p_0}{2} \quad .$$

Examination of this equation shows that ø will generally be less than 0.55 except when ä is very large, and/or the cov $(p_1, p_0) < 0$. In general, matching produces positive correlations and it can be expected that there will be less than 55% of case control pairs that are informative.

Tables 1 and 2 show the power of the proposed design to detect specified odds ratios as a function of the correlation (0.5 and 0.0) between case and control exposure rates, and the expected value of the control exposure rate with the alpha level for the test set at 0.05 (two sided test) and with 720 cases. With the proposed number of cases and controls there will be 98.6%

power to detect odds ratios of 0.7 or less and 98.8% power to detect odds ratios of 1.4 or greater when the correlation between case and control exposures is 0.5 (Table 1) and the proportion of controls exposed is 0.3. If the correlation between cases and control exposures is 0.0 (a conservative estimate), the power is reduced to 84.3% and 85.1%, respectively. If the proportion of controls exposed is reduced to 0.05 there is at least 90% power to detect an odds ratio of 2.0.

12.2.2 Power Calculations for Continuous Variables in the Case Control Study

Formulas for the calculation of study size and power for continuous variables have been developed by Walter (Walter, 1980) and by Lubin, Gail and Ershow (Lubin et al, 1988). Here, the derivations of Lubin et al. will be used to evaluate the operating characteristics of this study. The general sample size formula used in this evaluation is:

$$N = \frac{(\theta+1)}{\theta}\,\frac{[Z_\alpha\sigma_x+Z_\beta\{(\theta\sigma_1^2+\sigma_0^2)/(\theta+1)\}^{1/2}]^2}{(\mu_1-\mu_0)^2}$$

where

$$\sigma_\div^2 = (\sigma_1^2+\theta\sigma_0^2)/(\theta+1)+(\mu_1-\mu_0)^2\theta/(\theta+1)^2$$

and

$$\mu_i = \left\{\int_m xf(x)P(D=i*x)dx\right\}\left\{\int_m f(x)P(D=i*x)dx\right\}^{-1}$$

$$\sigma_i^2 = \left\{\int_m x^2f(x)P(D=i*x)dx\right\}\left\{\int_m f(x)P(D=i*x)dx\right\}^{-1} - \mu_i^2 \quad .$$

In the above formula, μ_1 and σ_1^2 are the mean variance of the case exposure variable and μ_0 and σ_0^2 are the mean and variance of the control exposure variable. The proposed number of cases and controls is large enough to detect small effects (either in terms of linear risk or in terms of exponential risk). As such, the above formula can be simplified to:

$$N = \frac{(\theta+1)(Z_\alpha+Z_\beta)^2\sigma^2}{\theta(\mu_1-\mu_0)^2}$$

This simplification occurs because as the effect size gets small, $ó^2_÷ ' ó^2_1 ' ó^2_0 ' ó^2$. This formula can be rearranged to determine the effect size $(\mu_1 \& \mu_0)/ó$ that can be detected with specified alpha level, power, and number of case control pairs. With the proposed of 720 cases and 720 controls, there will be better than 90% power to detect effect sizes of at least 0.16 standard deviations, a small effect size.

12.2.3 Subgroup Analyses

As part of ACCESS, Clinical Center investigators may want to make comparisons of cases and controls within certain strata. For instance, there could be comparisons of female cases and controls, comparisons of black cases and controls, and comparisons of erythema nodosum cases with their matched controls. Each of these subgroup comparisons will bring with it a different number of cases and controls and power for making comparisons. Effect sizes that could be detected in one subgroup analysis, might not be detected in another analysis. Power analyses have been performed for statistical comparisons that will be performed in subgroups representing 7%, 14%, 25%, 50% and 75% of the entire case control study population. These percentages may be representative of comparisons for a small substudy (7% and 14%), within a sarcoidosis category (20%), within a gender comparison (50%), and within the black population (75%, published reports put the percentage of sarcoidosis cases who are black between 60% and 80% in some cities). Power calculations for binary exposure variables when performing analyses in subgroups are presented in Tables 3 through 12. There is a substantial change in the odds ratios that can be detected with adequate power depending upon the number of cases in the subgroup. For instance, fixing the odds ratio at 0.7, the correlation between case-control response at 0.5, and the proportion of controls exposed at 0.3, there is 54.8%, 83.7% and 95.0% power to detect this odds ratio for 180, 360 and 540 case control pairs, respectively.

As part of each subgroup analysis, a statistical test will be performed to determine if the findings relating to exposures in one subgroup correspond to the findings in the complimentary subgroup (an interaction test). For instance if a risk factor is discovered for females, is that risk

factor also present and at the same level of magnitude in males or is it different. For binary exposure variables a matched case control regression model will be used with terms for the subgroup, the exposure, and the exposure-subgroup interaction in the model. For a case control design with one case and one control, the Cox Proportional Hazards model can be used by creating a dummy variable that always lists the case and "failing" first with control "censored" after the case "failure time". Power calculations for the factorial term in the Cox Model have been published (Peterson and George, 1993). In general the statistical efficiency of the interaction test is lower than the main effects test. For instance, with 50% of the population in one subgroup and 50% in the complimentary subgroup, the efficiency of the interaction test is one half that of the main effects test.

As an example, the current study design has at least 80% percent power to detect an odds ratio of 1.25 when the exposure variable of interest has a 30% prevalence and the test is being performed at the 5% alpha level. Now let us consider a statistical interaction test of an exposure between two groups. The test would be designed to determine if the ratio of the two odds ratios in the two groups were different or the same. Specifically, the interaction test is a test of whether the ratio of these two odds ratios is one. To be able to detect a ratio of the two odds ratios that is 1.25 or larger with 80% power with an exposure variable with a 30% prevalence and testing at the 5% alpha level would require twice the number of case control pairs or 1,440 cases. With 720 cases, there is at least 80% power to detect a ratio of two odds ratios on the order of magnitude of 1.38. This is not substantially different from the operating characteristics of the main effect comparisons. Thus there will be adequate power to detect small interactions with the proposed sample size.

For continuous variables, there is little impact on the power of proposed analyses to detect meaningful differences between case and control means in each of the above subgroup sizes. With 180 cases in a subgroup, it will be possible to detect differences of 0.34 standard deviations with 90% power when testing at alpha 0.05 (two sided test).

12.2.4 Statistical Power Considerations for the Clinical Course Study

For the clinical course study, investigators may assess if certain physiological measurements, such as the Forced Expiratory Volume in one second (FEV_1) are different among the five groups defined by sarcoidosis category. Other variables (such as indices of disease severity) may also be measured longitudinally for these groups. For simplicity, it will be assumed that the FEV_1 level is being analyzed. Measurements of FEV_1 will be made at baseline and two years. For the purpose of estimating the minimum power achievable in this study it will be assumed that each patient will provide one observation of FEV_1 after study entry. The study population will consist of a total of 240 cases; 48 in each of the five sarcoidosis subgroups.

The power evaluations for analysis of FEV_1 are based on a test for differences among normally distributed observations. The assumption of constant variance of the outcome variable within sarcoidosis subgroup is important for this test to be valid. If it is determined that this assumption is not true, a data transformation (such as a logarithmic transformation) will be used before the analysis proceeds.

There are ten possible pairwise comparisons that might be performed in the analyses of FEV_1. Let R_1, R_2, R_3, R_4 and R_5 be the means of FEV_1 levels in the five sarcoidosis groups. The alpha level for the six pairwise comparisons will be controlled at 0.05 by performing an F test of H_0:$E(R_1)=E(R_2)=E(R_3)=E(R_4)=E(R_5)$, versus the alternative that the expected value of at least one of the means is different. The significance of the F test will be assessed at the 0.05 alpha level. The ten pairwise comparisons will be made only if the global F test is significant. In this case, each comparison will be made at the 0.05/6, (6 = the combinations of 4 things taken 2 at a time), comparison-wise alpha level. Hayter (Hayter, 1986) has shown that this procedure will control the family-wise error rate as well as the experiment-wise error rate.

The within-individual correlation is important for power calculations in a longitudinal data analysis. This power is minimized when the within-individual correlation is one or if only one measurement is taken per person. If the within-individual correlation is one, taking two measurements is not different from taking one measurement per patient. If the within-individual

correlation decreases to zero, the repeated measures analysis increases the power to detect specified alternatives. It is advantageous to determine the worst case scenario (within-individual correlation =1) when making power assessments. Power will likely be higher than this worst case scenario.

Scheffé (Scheffé, 1959) has shown that the non-centrality parameter for the numerator chi-square is minimized when the expected values for the means in two of the above groups differ by Ä and the expected value for each of the remaining groups are exactly halfway between the other two expected values. In this case the noncentrality parameter for the numerator chi-square is dependent only on the value of Ä and ó (the within-group standard deviation of the end point). Specifically, one can use the following equation to calculate power curves for the proposed design:

$$\ddot{o}\ (1\&\hat{a})\ '\ \left[\frac{J}{2xI}\right]^{1/2}\ \ \ddot{A}/\acute{o}$$

where ö (1-â) is derived from the Pearson-Hartley tables (Scheffé, 1959) for $V_1 = 4$ and $V_2 = 235$ degrees of freedom; J is the number of individuals in each group (48); Éis the number of groups (I=5); and ó is the within-group standard deviation of the FEV_1 measurements.

Table 13 shows the power to detect specified differences Ä (in terms of standard deviation units, Ä/ó) with 70%, 80% and 90% power when testing at the 0.05 á level with 48 cases in each of the sarcoidosis categories. The proposed study size of 240 cases (48 in each sarcoidosis group) is sufficient (power $\geq$ 80%) to detect a difference in the two true FEV_1 means of 0.70 standard deviations or more.

12.3 DATA ANALYSIS

12.3.1 Data Monitoring Reports

The interim data monitoring reports will be prepared semi-annually and will include at a minimum the following tables:

1. A summary of case and control recruitment and follow-up of cases according to sarcoidosis stage and Clinical Center, including the number of cases screened and recruited, the number of controls matched to cases, the number of cases at various

stages of follow-up, the number of completed scheduled visits for cases, and the number of study measurements or procedures completed for each study visit.

2. Tabulations of average number of specimens collected according to sarcoidosis category and Clinical Center, including the number of cases who completed each visit. Differences among sarcoidosis stages will be tested using significance levels developed without regard to a sequential monitoring plan.
3. Longitudinal analyses of key exposure and outcome information by sarcoidosis category.
4. Performance of required specimen collection and procedures and case compliance with scheduled return visits to the Clinical Centers.
5. Tabulations of the number of adverse events for required procedures for cases.
6. Number of cases screened, and proportion of cases screened who were eligible for ACCESS according to age, gender, race or other demographic characteristics. Number and proportion of cases screened and found ineligible according to the criterion or criteria for eligibility which resulted in their exclusion.
7. Quality of submitted specimens to the central facilities and comparisons among clinics for key variable collection in ACCESS.

The content of each report will be discussed with the NHLBI Project Office staff and with the study leadership prior to preparation of the report and its distribution to the DSMB. Any other analyses requested by the NHLBI Project Office staff or the DSMB will be prepared and presented at the time of the DSMB meeting.

12.3.2 Analysis of the Case Control Study

12.3.2.1 Introduction

There has been extensive development of statistical methods for the analysis of case control studies. Most important for the proposed study are the regression methods as reported in Breslow and Day (Breslow and Day, 1980). There have been several reports about the importance of

including adjustment variables when performing case control analyses. Specifically, failure to include adjustment variables when performing case control analyses can lead to bias in estimating effects for other variables. Thus data analysis for case control studies is typically more complicated than analyses for clinical trials.

When performing an analysis of a case control study Breslow and Day report that confounding arises due to associations that cannot be removed by an appropriate study design alone. There are appropriate statistical methods (both parametric and non-parametric) that can be used to adjust for confounding effects in a case control design.

The first goal in a case control study is to fully understand the distributions of variables collected as part of the study, and how these variables may differ between cases and controls. As part of this understanding, detailed univariate analyses will be performed on each of the exposure variables collected in the case control study. These descriptive methods will include tabulations, presentation of means and standard deviations, and analyses for outlying observations. Frequently a categorization of a continuous variable may be beneficial in the conduct of a case control study since the exact nature of the risk relationship is unknown. Categorization allows flexibility in estimating a dose response relationship, and an easy way to visualize the data. It is recommended that this categorization should have more than two categories (preferably as many as five if sufficient data are available and natural divisions can be identified).

Once the data have been described, it will be important to develop analytical techniques that will allow for proper adjustment to control for confounding of observed results. Some methods for these analyses are presented below.

12.3.2.2 Matched Case Control Designs

Cases and controls will be matched with respect to the case's age (± five years), gender, and race. Random digit dialing may implicitly match cases and controls for geographical location. A matched design will be most appropriate for analyzing the data in this study.

Simple presentations of matched case control data should follow the methods outlined by Breslow and Day. Categorical data will be presented using a cross tabulation of the number of cases exposed versus the number of controls exposed. Standard chi-square analyses will not be performed on these tables. Instead, methods for estimating the odds ratio from McNemar's test will be used to estimate the measure of association. Since the proposed number of cases is large, it will be possible to estimate 95% confidence intervals using the binomial approximation. For continuous variables, presentation of means will be accomplished using a paired t-test. These analyses can be performed using Proc Means in SAS. This will have the effect of adjusting for the matching variables. A point estimate for the difference in case and control means will be obtained and a 95% confidence interval for the difference will be calculated using this procedure.

It will be important to adjust study results for confounding variables that could bias the results of the case control study. Analyses using one more exposure variable(s) will be performed using conditional logistic regression methods. This method can be used to estimate odds ratios for case-control studies.

Statistical analyses for probability inference based on these estimates can also be performed using conditional logistic regression (Breslow et al, 1978). This model is robust in the sense that it will allow for the inclusion of effect modifiers or risk factors. Effect modifiers are variables that change the exposure-risk odd ratios for the disease. It will not be possible to estimate odds ratios for age, gender, or race since these are matching variables. However, it will be possible to include interaction terms between gender, race, or age and other exposure variables to determine if the odds ratio estimates for these other variables are homogenous in males and females or blacks and whites. In some situations, analyses will be required to determine if one type of exposure (e.g., occupational) is associated with a genetic predisposition of sarcoidosis. These analyses will be done using the conditional logistic regression model in a matched case control format. Tests of the effect modification of the exposure will be done using an interaction variable in the conditional logistic model. Conditional logistic regression will be performed using the PHREG procedure in SAS.

12.3.3 Analyses of ACCESS Substudies

All of the proposed analysis plans for the ACCESS Substudies are identical to the plans presented in Section 12.3.2. Only the sample sizes may change and this was addressed in Section 12.2.

12.3.4 Analyses for the Clinical Course Study

A key feature of the clinical course study is the different length of time that cases will be followed. Cases will be recruited over a one-year time period, and will be followed for a maximum of two years.

It is planned to analyze follow-up data using: the Generalized Estimating Equations (Liang and Zeger, 1986; Zeger and Liang, 1986) program that runs under the SAS system using IML or the longitudinal data analysis methods of Laird and Ware (Laird and Ware, 1982), using Proc MIXED, a SAS procedure. Both of these models are robust in that they will allow for the inclusion of correlations and dependence structures in the serial data being collected for each of the cases. The models have the added advantage that the results are presented much like the results from more standard linear models. These models can be used to analyze outcome measures with continuous distributions, and outcomes that are binary or categorical. Both models will allow for the inclusion of fixed covariates or time-dependent covariates (variables that change over the course of time, and influence the risk of progression or regression of disease in accordance with these variations).

The dependent variables that can be structured in the form of a time-to-event, survival analysis techniques will be most appropriate for this type of analysis. Event rates could be calculated using Kaplan-Meier estimates (Kaplan and Meier, 1958), and confidence intervals can be obtained using Greenwood's formula (Greenwood, 1926). If multivariate analyses are contemplated, the Cox proportional hazards model (Cox, 1972) could be used to perform multivariate analyses. This model will also accommodate the inclusion of fixed and time-dependent covariates, and allows for differences in the length of time that cases will be in follow-up. Tests for

interactions can be included in all of the above models. Dependent variables of interest will include measures of progression and regression of sarcoidosis symptoms.

12.3.5 "Synthetic Case Control" Studies

The term "Synthetic Case Control Study" is not to be confused with the case control study being performed as part of ACCESS. A synthetic case control study or its close relative the case cohort study is used to search for associations between results of prospectively collected specimens and events without having to perform assays on each patient in the study (Mantel, 1973). Similarly, the study design can be used to determine prospectively subjects who have events of interest, and then to match "controls" who have not had events by that time period, and then to collect non-concurrent data to test for associations between the "exposure variable" and the case control status.

One goal of the clinical course study will be a search for the determinants of progression and regression of sarcoidosis. Another will be to determine if familial characteristics play a role in the development of these events. Both of these objectives can be achieved using a synthetic case control methodology. These methods are especially useful when the event rates of interest are low. As an example, specimens will be available from the Central Repository for both the routine collection time points and clinically indicated collection times in the follow-up study. As events of interest are observed in the Clinical Course study a "control" (a patient without the event at the time) would be matched to the patient with the event (the case) and the case control pair would be analyzed in the synthetic case control study. During the course of study additional new tests may be required by the Steering Committee. These tests can be performed on banked specimens.

It is possible to match more than one control to each case. The efficiency of the test statistic with N controls matched to a case increases in the following way:

Efficiency = N/(N+1).

A slightly different design from the case control design is the case cohort design. In the case cohort design, a particular cohort is selected to have special assays performed that will not be

performed on the entire study cohort. As a patient experiences an event of interest, that person is added to the cohort and assays for the affected individual are performed if he/she is not already in the cohort. At the conclusion of the study, an analytical model such as Cox proportional hazards model (Cox, 1972) or a longitudinal data analysis model is used to analyze the data. The sequential addition of the cases produces a bias in the standard error estimations of the estimated parameters, but procedures to adjust for this bias are available to account for this problem (Prentice, 1986).

The case cohort design is generally better than the case control design if a large number of end points will be studied. With case control methods the number of controls rises in rough proportion to the total of all events observed, while the size of the cohort (comparison group) in the case cohort design is fixed.

12.3.6 Missing Data

Missing data are almost unavoidable in any study. In some circumstances, data will be missing at random. If data are missing at random, there will be a loss in efficiency of the proposed analyses, but bias will not be introduced into the study by not accounting for the missing data. If data are not missing at random, there could be a bias in some of the estimation routines used in this study. For instance, cases with sarcoidosis who miss follow-up visits have less severe disease or disease regression as opposed to the cases who return for follow-up visits. If estimation of disease progression (or regression) was done using only the cases with follow-up information, the results would be biased. There are numerous methods to account for data that are not missing at random. One such method using propensity scores (Thompson, unpublished) is to collect information about all cases at the time of the baseline evaluation, and then to use this information to determine those cases with similar baseline characteristics. In the event that there are missing data for one of the cases, the statistical weight of the surrogate case can be increased, and a weighted analysis can be performed. Proc IML will be used to calculate the variance components since the usual variance estimates are negatively biased (Thompson, unpublished). Other methods have been developed which account for different patterns of missing data (Dawson and Lagakos,

1993). Still other methods involve the use of regression models to estimate the values of the missing data by jointly modeling the probability that data will be missing, and the expected value of the response (Wu and Carrol, 1988).

12.3.7 Checking the Assumptions for Regression Models

The regression models proposed in this study have several assumptions. One assumption in the logistic regression model is that the change in odds in relation to the exposure variable is exponential in nature. If the exposure variable is categorical, there will not be a problem in using the exponential model. However, if the exposure variable is a continuous variable, it will be necessary to determine if the response in the odds ratio is exponential with respect to a linear increase in exposure. This can be tested by adding higher order terms (such as quadratic and cubic terms) to the equation, and then testing to determine if the coefficients associated with these terms are significant. This could be accomplished using a likelihood ratio test. There will also be a need to determine if any interaction terms should be added to the model, or if the relationship between the exposure variables is adequately explained using a "main effects" model. Some interaction terms may be specified as part of the study design. Clinical Coordinating Center staff will discuss with the Steering Committee whether there should be routine searches for higher order interactions. Harrel (Harrell et al, 1985) recommends that second order interactions should be a concern when developing logistic regression models, but that higher order interactions are rare, and should not be routinely placed in the regression equations. However, the incorporation of all second order interactions would require many regression coefficients which could cause problems in the estimation programs. Care will be necessary in specifying interaction terms for these analyses.

There are analogous procedures for testing some of the assumptions for the Cox proportional hazards model, and the longitudinal data analysis models. However, the Cox model has the added assumption that hazards are proportional. This assumption can be evaluated by adding time by covariate interaction terms and testing whether the coefficients for these terms are larger than could be expected by chance (Carter et al, 1983).

The assumptions of constant variance in linear models has been circumvented in the proposed longitudinal data analysis models. The models proposed all have robust estimation methods, that is, quasi-likelihood techniques (McCullach and Nelder, 1989), as part of the programming.

12.4 CONCLUSIONS

The methods for the major analyses for the case control study and the clinical course are presented in this chapter. For the case control study of cases with sarcoidosis and age-gender-race matched controls, a matched case control design has been proposed. Key issues in this design are control of bias and confounding. Control of confounding primarily depends upon the selection of adequate adjustment techniques. The proposed approach is to use non-parametric techniques such as the Mantel-Haenzel test for matched pairs, and conditional logistic regression for more complex analyses. For measurements that will be collected serially over time, longitudinal data analysis methods have been proposed. These methods are robust in that they will allow for differential numbers of observations for each case, correct for missing data, and unanticipated variance-covariance structures for the repeated measurements without loss of statistical validity in testing.

A preliminary power analysis has been performed for the proposed study. It has been found that the proposed number of cases and controls (at least 720 and 720) is sufficient to allow for small effects to be detected with adequate power (90%) when testing at the alpha level of 0.05 (two-sided tests). The proposed number of cases and controls is large enough to allow for subgroup analyses. The proposed number of cases is also sufficient to allow for the detection of moderate differences in means in the longitudinal follow-up study. There will be adequate power to detect small effect sizes (0.70 ó) when testing at the 0.05 level and when making comparison of the five sarcoidosis groups.

Table 1
Power of Case - Control Comparisons
alpha=0.05 and N=720
Correlation (p1,p0)=0.5

Odds Ratio	Proportion of Controls Exposed							
	0.01	0.025	0.05	0.1	0.3	0.5	0.7	0.9
0.3	0.580	0.927	0.998	1.000	1.000	1.000	1.000	1.000
0.5	0.324	0.658	0.914	0.996	1.000	1.000	1.000	1.000
0.6	0.217	0.458	0.739	0.951	1.000	1.000	1.000	0.993
0.7	0.136	0.273	0.477	0.751	0.986	0.997	0.994	0.860
0.8	0.081	0.141	0.234	0.401	0.760	0.844	0.796	0.463
0.9	0.046	0.063	0.087	0.129	0.248	0.292	0.257	0.137
1.0	0.025	0.025	0.025	0.025	0.025	0.025	0.025	0.025
1.1	0.045	0.060	0.082	0.119	0.218	0.247	0.212	0.114
1.2	0.073	0.122	0.197	0.329	0.623	0.682	0.592	0.291
1.3	0.112	0.213	0.366	0.599	0.907	0.936	0.876	0.512
1.4	0.160	0.327	0.556	0.817	0.988	0.993	0.976	0.706
1.5	0.217	0.454	0.725	0.936	0.999	1.000	0.997	0.841
1.6	0.282	0.579	0.849	0.982	1.000	1.000	1.000	0.920
1.7	0.351	0.692	0.926	0.996	1.000	1.000	1.000	0.962
1.8	0.421	0.785	0.967	0.999	1.000	1.000	1.000	0.982
1.9	0.492	0.856	0.987	1.000	1.000	1.000	1.000	0.992
2.0	0.559	0.908	0.995	1.000	1.000	1.000	1.000	0.996
3.0	0.940	1.000	1.000	1.000	1.000	1.000	1.000	1.000
4.0	0.995	1.000	1.000	1.000	1.000	1.000	1.000	1.000
5.0	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
10	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
15	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
20	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000

Table 2
Power of Case - Control Comparisons
alpha=0.05 and N=720
Correlation (p1,p0)=0

Odds Ratio	Proportion of Controls Exposed							
	0.01	0.025	0.05	0.1	0.3	0.5	0.7	0.9
0.3	0.376	0.737	0.955	0.999	1.000	1.000	1.000	1.000
0.5	0.193	0.406	0.676	0.921	1.000	1.000	1.000	0.993
0.6	0.133	0.265	0.463	0.738	0.986	0.997	0.996	0.889
0.7	0.089	0.160	0.273	0.468	0.843	0.917	0.889	0.582
0.8	0.059	0.091	0.139	0.227	0.472	0.559	0.507	0.263
0.9	0.039	0.049	0.062	0.085	0.146	0.168	0.150	0.089
1.0	0.025	0.025	0.025	0.025	0.025	0.025	0.025	0.025
1.1	0.038	0.047	0.060	0.080	0.131	0.145	0.127	0.077
1.2	0.055	0.081	0.120	0.188	0.363	0.407	0.342	0.168
1.3	0.076	0.128	0.208	0.348	0.644	0.697	0.599	0.292
1.4	0.102	0.188	0.321	0.531	0.851	0.885	0.801	0.429
1.5	0.132	0.260	0.447	0.700	0.952	0.967	0.917	0.561
1.6	0.166	0.340	0.573	0.829	0.988	0.992	0.970	0.675
1.7	0.204	0.424	0.688	0.912	0.997	0.998	0.990	0.766
1.8	0.246	0.509	0.783	0.959	1.000	1.000	0.997	0.835
1.9	0.289	0.591	0.856	0.983	1.000	1.000	0.999	0.885
2.0	0.335	0.666	0.909	0.993	1.000	1.000	1.000	0.921
3.0	0.753	0.983	1.000	1.000	1.000	1.000	1.000	0.998
4.0	0.942	1.000	1.000	1.000	1.000	1.000	1.000	1.000
5.0	0.990	1.000	1.000	1.000	1.000	1.000	1.000	1.000
10	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
15	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
20	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000

Table 3
Power of Case - Control Comparisons
alpha=0.05 and N=540
Correlation (p1,p0)=0.5

Odds Ratio	Proportion of Controls Exposed							
	0.01	0.025	0.05	0.1	0.3	0.5	0.7	0.9
0.3	0.465	0.840	0.986	1.000	1.000	1.000	1.000	1.000
0.5	0.255	0.536	0.821	0.980	1.000	1.000	1.000	1.000
0.6	0.174	0.361	0.615	0.880	0.999	1.000	1.000	0.970
0.7	0.113	0.216	0.377	0.628	0.950	0.983	0.972	0.750
0.8	0.070	0.116	0.187	0.316	0.636	0.730	0.675	0.366
0.9	0.042	0.056	0.075	0.107	0.197	0.230	0.204	0.113
1.0	0.025	0.025	0.025	0.025	0.025	0.025	0.025	0.025
1.1	0.041	0.054	0.071	0.100	0.174	0.197	0.170	0.095
1.2	0.064	0.102	0.158	0.259	0.503	0.559	0.475	0.230
1.3	0.094	0.170	0.288	0.481	0.811	0.855	0.769	0.406
1.4	0.131	0.258	0.444	0.698	0.954	0.970	0.927	0.582
1.5	0.174	0.358	0.601	0.854	0.993	0.996	0.982	0.727
1.6	0.223	0.464	0.736	0.940	0.999	1.000	0.996	0.831
1.7	0.276	0.568	0.839	0.979	1.000	1.000	0.999	0.899
1.8	0.332	0.663	0.908	0.994	1.000	1.000	1.000	0.941
1.9	0.390	0.745	0.951	0.998	1.000	1.000	1.000	0.966
2.0	0.447	0.812	0.975	1.000	1.000	1.000	1.000	0.980
3.0	0.860	0.997	1.000	1.000	1.000	1.000	1.000	1.000
4.0	0.976	1.000	1.000	1.000	1.000	1.000	1.000	1.000
5.0	0.997	1.000	1.000	1.000	1.000	1.000	1.000	1.000
10	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
15	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
20	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000

Table 4
Power of Case - Control Comparisons
alpha=0.05 and N=540
Correlation (p1,p0)=0

Odds Ratio	Proportion of Controls Exposed							
	0.01	0.025	0.05	0.1	0.3	0.5	0.7	0.9
0.3	0.296	0.613	0.886	0.993	1.000	1.000	1.000	1.000
0.5	0.155	0.319	0.553	0.831	0.997	1.000	1.000	0.970
0.6	0.110	0.210	0.366	0.614	0.948	0.984	0.978	0.787
0.7	0.077	0.131	0.216	0.370	0.729	0.826	0.787	0.467
0.8	0.053	0.078	0.115	0.181	0.373	0.447	0.402	0.208
0.9	0.037	0.045	0.056	0.073	0.120	0.137	0.123	0.076
1.0	0.025	0.025	0.025	0.025	0.025	0.025	0.025	0.025
1.1	0.036	0.044	0.054	0.069	0.108	0.119	0.106	0.067
1.2	0.050	0.071	0.100	0.152	0.286	0.321	0.269	0.137
1.3	0.066	0.107	0.167	0.274	0.523	0.573	0.482	0.231
1.4	0.086	0.152	0.253	0.423	0.738	0.782	0.681	0.339
1.5	0.109	0.206	0.353	0.576	0.881	0.908	0.826	0.449
1.6	0.135	0.268	0.459	0.712	0.954	0.967	0.914	0.552
1.7	0.164	0.334	0.564	0.819	0.985	0.989	0.960	0.643
1.8	0.195	0.404	0.661	0.894	0.995	0.997	0.983	0.719
1.9	0.229	0.475	0.745	0.942	0.999	0.999	0.993	0.782
2.0	0.264	0.543	0.814	0.970	1.000	1.000	0.997	0.831
3.0	0.629	0.943	0.998	1.000	1.000	1.000	1.000	0.986
4.0	0.864	0.997	1.000	1.000	1.000	1.000	1.000	0.998
5.0	0.959	1.000	1.000	1.000	1.000	1.000	1.000	1.000
10	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
15	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
20	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000

Table 5
Power of Case - Control Comparisons
alpha=0.05 and N=360
Correlation (p1,p0)=0.5

Odds Ratio	Proportion of Controls Exposed							
	0.01	0.025	0.05	0.1	0.3	0.5	0.7	0.9
0.3	0.333	0.674	0.925	0.997	1.000	1.000	1.000	1.000
0.5	0.185	0.387	0.652	0.906	1.000	1.000	1.000	0.991
0.6	0.130	0.258	0.452	0.725	0.983	0.997	0.995	0.880
0.7	0.089	0.159	0.269	0.463	0.837	0.913	0.885	0.576
0.8	0.059	0.091	0.139	0.226	0.470	0.556	0.504	0.261
0.9	0.039	0.049	0.062	0.085	0.146	0.168	0.150	0.089
1.0	0.025	0.025	0.025	0.025	0.025	0.025	0.025	0.025
1.1	0.038	0.047	0.060	0.080	0.130	0.145	0.127	0.077
1.2	0.055	0.081	0.120	0.187	0.362	0.406	0.341	0.168
1.3	0.076	0.128	0.207	0.345	0.641	0.693	0.596	0.290
1.4	0.101	0.186	0.317	0.526	0.846	0.881	0.796	0.425
1.5	0.130	0.256	0.440	0.691	0.948	0.964	0.912	0.553
1.6	0.163	0.332	0.562	0.819	0.986	0.991	0.966	0.663
1.7	0.199	0.413	0.673	0.903	0.997	0.998	0.988	0.752
1.8	0.238	0.493	0.766	0.952	0.999	1.000	0.996	0.820
1.9	0.278	0.570	0.839	0.978	1.000	1.000	0.999	0.870
2.0	0.320	0.642	0.893	0.991	1.000	1.000	1.000	0.906
3.0	0.699	0.970	0.999	1.000	1.000	1.000	1.000	0.995
4.0	0.897	0.999	1.000	1.000	1.000	1.000	1.000	0.999
5.0	0.968	1.000	1.000	1.000	1.000	1.000	1.000	1.000
10	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
15	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
20	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000

Table 6
Power of Case - Control Comparisons
alpha=0.05 and N=360
Correlation (p1,p0)=0

Odds Ratio	Proportion of Controls Exposed							
	0.01	0.025	0.05	0.1	0.3	0.5	0.7	0.9
0.3	0.213	0.450	0.734	0.952	1.000	1.000	1.000	1.000
0.5	0.118	0.229	0.401	0.664	0.971	0.994	0.993	0.880
0.6	0.087	0.154	0.261	0.451	0.834	0.918	0.900	0.614
0.7	0.064	0.101	0.158	0.264	0.555	0.658	0.614	0.335
0.8	0.047	0.065	0.090	0.135	0.267	0.319	0.287	0.153
0.9	0.034	0.041	0.049	0.061	0.093	0.105	0.096	0.063
1.0	0.025	0.025	0.025	0.025	0.025	0.025	0.025	0.025
1.1	0.034	0.040	0.047	0.058	0.086	0.093	0.084	0.057
1.2	0.044	0.059	0.080	0.115	0.206	0.230	0.194	0.105
1.3	0.056	0.084	0.125	0.198	0.377	0.417	0.346	0.168
1.4	0.070	0.115	0.183	0.302	0.564	0.609	0.510	0.242
1.5	0.086	0.152	0.252	0.419	0.727	0.765	0.658	0.321
1.6	0.104	0.193	0.329	0.539	0.846	0.872	0.775	0.400
1.7	0.123	0.239	0.410	0.650	0.920	0.936	0.859	0.476
1.8	0.144	0.289	0.491	0.745	0.962	0.969	0.914	0.546
1.9	0.167	0.340	0.571	0.822	0.983	0.986	0.949	0.609
2.0	0.191	0.393	0.644	0.880	0.993	0.994	0.971	0.664
3.0	0.464	0.824	0.976	0.999	1.000	1.000	1.000	0.925
4.0	0.704	0.969	0.999	1.000	1.000	1.000	1.000	0.978
5.0	0.856	0.996	1.000	1.000	1.000	1.000	1.000	0.991
10	0.998	1.000	1.000	1.000	1.000	1.000	1.000	0.999
15	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
20	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000

Table 7
Power of Case - Control Comparisons
alpha=0.05 and N=180
Correlation (p1,p0)=0.5

Odds Ratio	Proportion of Controls Exposed							
	0.01	0.025	0.05	0.1	0.3	0.5	0.7	0.9
0.3	0.190	0.400	0.671	0.920	1.000	1.000	1.000	1.000
0.5	0.113	0.219	0.383	0.640	0.963	0.992	0.990	0.862
0.6	0.085	0.151	0.255	0.440	0.823	0.910	0.891	0.601
0.7	0.063	0.100	0.157	0.261	0.548	0.651	0.608	0.330
0.8	0.047	0.064	0.090	0.134	0.265	0.318	0.285	0.152
0.9	0.034	0.040	0.049	0.061	0.093	0.105	0.096	0.063
1.0	0.025	0.025	0.025	0.025	0.025	0.025	0.025	0.025
1.1	0.034	0.040	0.047	0.058	0.085	0.093	0.084	0.057
1.2	0.044	0.059	0.080	0.115	0.205	0.229	0.194	0.105
1.3	0.056	0.084	0.125	0.196	0.375	0.414	0.343	0.167
1.4	0.070	0.114	0.181	0.298	0.558	0.603	0.504	0.239
1.5	0.085	0.150	0.248	0.413	0.719	0.757	0.649	0.316
1.6	0.102	0.189	0.321	0.528	0.836	0.863	0.764	0.391
1.7	0.121	0.233	0.398	0.635	0.912	0.928	0.847	0.463
1.8	0.140	0.279	0.476	0.728	0.955	0.964	0.903	0.529
1.9	0.161	0.327	0.551	0.803	0.978	0.982	0.940	0.588
2.0	0.183	0.376	0.620	0.862	0.990	0.992	0.963	0.640
3.0	0.419	0.775	0.959	0.998	1.000	1.000	1.000	0.891
4.0	0.625	0.938	0.997	1.000	1.000	1.000	1.000	0.952
5.0	0.770	0.985	1.000	1.000	1.000	1.000	1.000	0.972
10	0.984	1.000	1.000	1.000	1.000	1.000	1.000	0.990
15	0.999	1.000	1.000	1.000	1.000	1.000	1.000	0.992
20	1.000	1.000	1.000	1.000	1.000	1.000	1.000	0.993

Table 8
Power of Case - Control Comparisons
alpha=0.05 and N=180
Correlation (p1,p0)=0

Odds Ratio	Proportion of Controls Exposed							
	0.01	0.025	0.05	0.1	0.3	0.5	0.7	0.9
0.3	0.128	0.254	0.447	0.727	0.989	0.999	1.000	0.982
0.5	0.079	0.136	0.226	0.392	0.777	0.885	0.876	0.601
0.6	0.062	0.098	0.152	0.254	0.545	0.660	0.630	0.356
0.7	0.049	0.070	0.100	0.154	0.317	0.387	0.356	0.190
0.8	0.039	0.050	0.064	0.088	0.155	0.182	0.166	0.097
0.9	0.031	0.035	0.040	0.048	0.066	0.072	0.067	0.049
1.0	0.025	0.025	0.025	0.025	0.025	0.025	0.025	0.025
1.1	0.031	0.035	0.039	0.046	0.062	0.066	0.061	0.045
1.2	0.038	0.047	0.058	0.077	0.124	0.136	0.118	0.072
1.3	0.045	0.061	0.083	0.120	0.213	0.235	0.196	0.105
1.4	0.053	0.078	0.113	0.173	0.323	0.352	0.289	0.143
1.5	0.062	0.097	0.148	0.236	0.442	0.475	0.387	0.183
1.6	0.071	0.118	0.187	0.307	0.558	0.591	0.484	0.226
1.7	0.082	0.141	0.231	0.381	0.663	0.691	0.574	0.269
1.8	0.093	0.166	0.278	0.457	0.752	0.774	0.653	0.311
1.9	0.104	0.193	0.327	0.531	0.822	0.837	0.721	0.352
2.0	0.116	0.222	0.377	0.601	0.876	0.885	0.777	0.392
3.0	0.262	0.534	0.796	0.957	0.998	0.997	0.978	0.672
4.0	0.423	0.774	0.955	0.997	1.000	1.000	0.997	0.802
5.0	0.570	0.903	0.992	1.000	1.000	1.000	0.999	0.865
10	0.934	0.999	1.000	1.000	1.000	1.000	1.000	0.952
15	0.992	1.000	1.000	1.000	1.000	1.000	1.000	0.969
20	0.999	1.000	1.000	1.000	1.000	1.000	1.000	0.975

Table 9
Power of Case - Control Comparisons
alpha=0.05 and N=100
Correlation (p1,p0)=0.5

Odds Ratio	Proportion of Controls Exposed							
	0.01	0.025	0.05	0.1	0.3	0.5	0.7	0.9
0.3	0.124	0.245	0.433	0.709	0.986	0.999	0.999	0.978
0.5	0.081	0.141	0.236	0.408	0.797	0.900	0.891	0.622
0.6	0.064	0.102	0.161	0.270	0.576	0.692	0.662	0.379
0.7	0.051	0.073	0.105	0.164	0.341	0.417	0.384	0.204
0.8	0.040	0.051	0.067	0.093	0.167	0.197	0.178	0.103
0.9	0.032	0.036	0.041	0.049	0.069	0.076	0.070	0.051
1.0	0.025	0.025	0.025	0.025	0.025	0.025	0.025	0.025
1.1	0.031	0.035	0.040	0.048	0.064	0.069	0.063	0.047
1.2	0.038	0.048	0.061	0.082	0.133	0.146	0.126	0.076
1.3	0.046	0.063	0.087	0.128	0.230	0.254	0.212	0.112
1.4	0.055	0.081	0.120	0.186	0.348	0.380	0.312	0.152
1.5	0.064	0.102	0.157	0.253	0.473	0.508	0.415	0.196
1.6	0.074	0.124	0.199	0.327	0.591	0.624	0.515	0.241
1.7	0.085	0.148	0.245	0.404	0.694	0.722	0.604	0.285
1.8	0.096	0.175	0.293	0.481	0.778	0.799	0.681	0.328
1.9	0.108	0.202	0.343	0.554	0.843	0.858	0.745	0.370
2.0	0.120	0.231	0.393	0.622	0.891	0.900	0.797	0.408
3.0	0.257	0.525	0.788	0.953	0.998	0.997	0.975	0.663
4.0	0.397	0.742	0.941	0.995	1.000	1.000	0.995	0.771
5.0	0.521	0.866	0.984	0.999	1.000	1.000	0.998	0.822
10	0.865	0.995	1.000	1.000	1.000	1.000	1.000	0.892
15	0.963	1.000	1.000	1.000	1.000	1.000	1.000	0.905
20	0.989	1.000	1.000	1.000	1.000	1.000	1.000	0.909

Table 10
Power of Case - Control Comparisons
alpha=0.05 and N=100
Correlation (p1,p0)=0

Odds Ratio	Proportion of Controls Exposed							
	0.01	0.025	0.05	0.1	0.3	0.5	0.7	0.9
0.3	0.089	0.160	0.275	0.480	0.886	0.968	0.976	0.857
0.5	0.060	0.094	0.145	0.241	0.528	0.654	0.641	0.379
0.6	0.050	0.072	0.103	0.161	0.339	0.424	0.400	0.219
0.7	0.042	0.055	0.073	0.104	0.196	0.238	0.220	0.125
0.8	0.035	0.042	0.051	0.066	0.105	0.120	0.111	0.071
0.9	0.030	0.032	0.036	0.041	0.052	0.056	0.053	0.042
1.0	0.025	0.025	0.025	0.025	0.025	0.025	0.025	0.025
1.1	0.029	0.032	0.035	0.040	0.050	0.052	0.049	0.039
1.2	0.034	0.040	0.048	0.059	0.087	0.094	0.084	0.056
1.3	0.039	0.049	0.063	0.085	0.137	0.150	0.128	0.076
1.4	0.044	0.060	0.080	0.115	0.200	0.217	0.180	0.098
1.5	0.050	0.071	0.100	0.151	0.271	0.293	0.238	0.121
1.6	0.056	0.083	0.123	0.191	0.348	0.371	0.298	0.144
1.7	0.062	0.097	0.147	0.234	0.427	0.450	0.359	0.169
1.8	0.069	0.111	0.174	0.281	0.503	0.524	0.418	0.193
1.9	0.075	0.126	0.202	0.329	0.575	0.593	0.475	0.217
2.0	0.083	0.142	0.232	0.379	0.641	0.654	0.528	0.241
3.0	0.165	0.331	0.547	0.782	0.952	0.942	0.841	0.434
4.0	0.260	0.524	0.778	0.942	0.994	0.989	0.937	0.553
5.0	0.357	0.681	0.901	0.985	0.999	0.997	0.970	0.627
10	0.734	0.969	0.998	1.000	1.000	1.000	0.996	0.770
15	0.903	0.997	1.000	1.000	1.000	1.000	0.998	0.813
20	0.966	1.000	1.000	1.000	1.000	1.000	0.999	0.832

Table 11
Power of Case - Control Comparisons
alpha=0.05 and N=50
Correlation (p1,p0)=0.5

Odds Ratio	Proportion of Controls Exposed							
	0.01	0.025	0.05	0.1	0.3	0.5	0.7	0.9
0.3	0.082	0.144	0.244	0.427	0.837	0.943	0.956	0.804
0.5	0.059	0.091	0.139	0.230	0.505	0.630	0.617	0.362
0.6	0.050	0.071	0.101	0.157	0.330	0.413	0.390	0.214
0.7	0.042	0.055	0.072	0.103	0.194	0.235	0.217	0.123
0.8	0.035	0.042	0.051	0.066	0.104	0.120	0.110	0.071
0.9	0.030	0.032	0.036	0.041	0.052	0.056	0.053	0.042
1.0	0.025	0.025	0.025	0.025	0.025	0.025	0.025	0.025
1.1	0.029	0.032	0.035	0.040	0.050	0.052	0.049	0.039
1.2	0.034	0.040	0.048	0.059	0.087	0.094	0.083	0.056
1.3	0.039	0.049	0.063	0.084	0.137	0.149	0.127	0.076
1.4	0.044	0.059	0.080	0.114	0.198	0.215	0.178	0.097
1.5	0.050	0.070	0.099	0.148	0.267	0.288	0.234	0.119
1.6	0.055	0.082	0.121	0.187	0.341	0.363	0.292	0.142
1.7	0.061	0.095	0.144	0.228	0.415	0.437	0.349	0.165
1.8	0.067	0.108	0.169	0.272	0.487	0.508	0.405	0.187
1.9	0.074	0.122	0.195	0.316	0.555	0.572	0.457	0.209
2.0	0.080	0.137	0.222	0.362	0.617	0.630	0.505	0.230
3.0	0.150	0.298	0.497	0.730	0.925	0.913	0.793	0.391
4.0	0.224	0.454	0.702	0.897	0.983	0.972	0.890	0.480
5.0	0.295	0.583	0.827	0.959	0.995	0.988	0.929	0.532
10	0.582	0.894	0.984	0.999	1.000	0.998	0.971	0.618
15	0.755	0.969	0.997	1.000	1.000	0.999	0.977	0.638
20	0.854	0.989	0.999	1.000	1.000	0.999	0.980	0.644

Table 12
Power of Case - Control Comparisons
alpha=0.05 and N=50
Correlation (p1,p0)=0

Odds Ratio	Proportion of Controls Exposed							
	0.01	0.025	0.05	0.1	0.3	0.5	0.7	0.9
0.3	0.063	0.101	0.159	0.271	0.610	0.768	0.796	0.572
0.5	0.047	0.066	0.093	0.142	0.300	0.385	0.375	0.214
0.6	0.041	0.054	0.071	0.101	0.193	0.239	0.226	0.131
0.7	0.036	0.044	0.054	0.072	0.119	0.141	0.131	0.082
0.8	0.032	0.036	0.042	0.050	0.072	0.080	0.075	0.054
0.9	0.028	0.030	0.032	0.036	0.043	0.045	0.043	0.036
1.0	0.025	0.025	0.025	0.025	0.025	0.025	0.025	0.025
1.1	0.028	0.030	0.032	0.035	0.041	0.043	0.041	0.034
1.2	0.031	0.035	0.040	0.047	0.062	0.066	0.060	0.045
1.3	0.034	0.041	0.049	0.061	0.089	0.095	0.084	0.056
1.4	0.038	0.047	0.059	0.077	0.121	0.130	0.111	0.068
1.5	0.041	0.053	0.070	0.096	0.158	0.169	0.140	0.080
1.6	0.045	0.060	0.082	0.116	0.198	0.210	0.172	0.093
1.7	0.048	0.068	0.094	0.139	0.240	0.253	0.204	0.105
1.8	0.052	0.075	0.108	0.163	0.285	0.298	0.236	0.118
1.9	0.056	0.083	0.122	0.188	0.330	0.342	0.268	0.130
2.0	0.060	0.092	0.137	0.214	0.375	0.385	0.300	0.142
3.0	0.103	0.189	0.312	0.491	0.726	0.705	0.552	0.244
4.0	0.152	0.298	0.487	0.704	0.884	0.851	0.695	0.315
5.0	0.202	0.405	0.632	0.833	0.946	0.915	0.775	0.365
10	0.448	0.772	0.935	0.987	0.995	0.983	0.902	0.479
15	0.635	0.914	0.985	0.998	0.999	0.992	0.932	0.521
20	0.762	0.965	0.996	0.999	0.999	0.995	0.944	0.543

Table 13

Maximum Effect Size That Can Be Detected With Specific Power
Analysis of Variance
(One Comparison á = 0.05)
(N = 240)

Power	70%	80%	90%
Ä/ó	0.62	0.70	0.80

CHAPTER 13

TRAINING AND CERTIFICATION PROCEDURES

13.1 INTRODUCTION

Each ACCESS Clinical Center must be certified for screening patients and performing physical examinations and spirometry in order to recruit and examine cases and controls for ACCESS. The staff who will be performing ACCESS test procedures, interviewing ACCESS cases and controls, and completing ACCESS data collection forms and performing data entry must attend a training session or be trained by a certified person and demonstrate proficiency in the procedures they will perform during the study in order to be certified.

13.2 CLINICAL CENTER CERTIFICATION

In order for an ACCESS Clinical Center to be certified to screen cases, the Clinical Center must submit to the Clinical Coordinating Center (CCC) documentation of Institutional Review Board (IRB) approval of the ACCESS Protocol and Consent Forms. Copies of the Consent Forms were submitted before recruitment was started and whenever the forms are revised. Notification of IRB approval in each Clinical Center is also required annually. Conflict of Interest Statements (see Chapter 5) for appropriate ACCESS staff members are required for certification and these forms are to be submitted annually. In addition, the ACCESS Clinical Center must have at least one certified research coordinator, one physician certified to perform physical examinations, one individual certified to perform data entry, one individual certified to use the ATRS, and a certified Spirometry Laboratory.

In order to be certified to enroll cases and controls into ACCESS, the Clinical Center must have the facilities and staff to collect, analyze and ship blood specimens and certified staff to interview cases and controls and to operate the distributed data management system at the Clinical Center.

13.2.1 Spirometry Laboratory

The Spirometry Laboratory in the Clinical Center Pulmonary Function Laboratory should adhere to the American Thoracic Society standards (Crapo et al, 1995) for performance and quality control of spirometry. The quality control procedures for performing spirometry in the local Pulmonary Function Laboratory should be documented in a log as follows:

a) 3L calibration syringe check daily;

b) Leak check daily;

c) Linearity check weekly;

d) Repeat spirometry performed on healthy lab staff member(s) or other volunteer(s) to check for consistency monthly; and

e) Spirometry thermistor compared to a reference thermometer monthly.

This log must be available for review during site visits.

Each set of tracings for the ACCESS cases are to be reviewed by the Clinical Center Principal Investigator or designated Co-Investigator to determine that there is less than 5% variability among the three tracings for each patient. The spirometry tracings for the first three patients enrolled in each Clinical Center are requested by Clinical Coordinating Center staff who arrange for quality assurance review of those tracings.

13.3 CERTIFICATION OF INDIVIDUAL ACCESS STAFF MEMBERS AND FACILITIES

13.3.1 Research Coordinator / Interviewer

In order for a person to be certified as a Research Coordinator / Interviewer in ACCESS, the person must attend a training session, or be trained and tested by a certified Research Coordinator / Interviewer. The certification process includes a test on the methods and procedures of ACCESS and knowledge of the ACCESS interviewing procedures. The person completes one successful practice session registering a case or control using the Automated Telephone Response System (ATRS). The person completes and submits to the CCC two copies each of the ACCESS Demographics and Medical History Questionnaire (Form 10),

Family History Questionnaire (Form 22), and the Occupational and Recreational Questionnaire (Form 12) using data from sarcoidosis patients known at the Clinical Center. The completed forms are submitted with a completed Request for Certification.

13.3.2 Physical Examination Physician

The Principal Investigator of an ACCESS Clinical Unit notifies the Clinical Coordinating Center that an ACCESS physician is certified to perform physical examinations on ACCESS patients by signifying that the physician understands the ACCESS protocol, including the procedures that he/she is to perform and has taken a test on the methods and procedures associated with the ACCESS protocol.

13.3.3 Data Entry Personnel

The individuals certified to enter data using the distributed data management system may be research coordinators or other designated Clinical Center staff.

It is the responsibility of the Clinical Center Principal Investigator to determine who is responsible for collecting data, and who is responsible for entering data into the ACCESS database. The person responsible for entering data must attend a training session or be trained by a certified data entry person. Once trained, the candidate must enter data for two forms each of the: Demographics and Medical History Questionnaire (Form 10), the Family History Questionnaire (Form 22), and the Occupational and Recreational Questionnaire (Form 12) using completed forms from the CCC that are sent to the Data Entry Applicant. These data and applicant information are electronically transferred to the CCC during regularly scheduled data transmission. The records generated from the practice forms are compared to the study standard forms at the CCC, and the applicant is notified of any discrepancies. Once the material has been received in a satisfactory format, the Clinical Center Principal Investigator is notified that the Data Entry Applicant has been certified and a permanent certification number is assigned.

13.3.4 ATRS Staff

C-TASC staff have established a system to allow authorized personnel to practice a few registrations without actually entering a case. The same procedures are used for this practice session as for an actual registration except that: when requested to enter the Clinic Password, enter 9999 rather than the Clinic Password that has been assigned to the Clinical Center. The ATRS identifies this call as a practice session. Follow the instructions as if a case were actually being registered or enrolled. Use 999-9999 as the practice ID number. Each individual authorized to register or enroll patients should practice at least once to be certified to use the system for cases and controls. The practice session should be performed during working hours, weekdays 9:00 a.m. - 4:00 p.m. so that problems can be resolved if they occur. At the end of the practice session, the system indicates the status of the practice session. The practice system will remain in place for the duration of the study. If Clinical Center staff think they need some practice using the system after certification, or if new personnel are assigned to register cases and controls, the practice system can be used for this purpose.

13.4 RESPONSIBILITIES OF THE CLINICAL COORDINATING CENTER IN TRAINING AND CERTIFICATION

The responsibilities of the Clinical Coordinating Center in training and certification are as follows:

1. Assist in organization and presentation of training sessions.
2. Review of forms submitted by ACCESS personnel as part of certification requirements and communication of concerns to those personnel.
3. Coordinate results of review of certification materials submitted by personnel at Clinical Centers.
4. Maintain documentation of the various aspects of certification requirements which have been completed or need to be completed by Clinical Centers and individual staff.
5. Issue certification numbers to certified individuals.

CHAPTER 14

QUALITY ASSESSMENT PROCEDURES

14.1 INTRODUCTION

A primary concern for every study is to assure the quality of data being collected and analyzed. The validity of the reports and results produced and published by the study depends upon the integrity of the data submitted by the Clinical Centers and core facilities and upon the appropriateness, thoroughness, and correctness of the data processing and data analysis procedures carried out by the Clinical Coordinating Center (CCC) staff. The first step in assuring quality data is to have the data collectors and observers properly trained, certified and periodically recertified. Standard procedures for pulmonary function testing and bronchoalveolar lavage (BAL) specimen processing are used in this study. This is supplemented with various procedures to monitor the performance of staff with respect to the quality of the study data they have reported. The CCC staff implemented a quality assurance plan developed in collaboration with the Steering Committee and NHLBI. Procedures for monitoring the performance and quality of submitted data and specimens from the Clinical Centers, the core facilities, and the Clinical Coordinating Center are given in the following sections.

14.2 QUALITY ASSESSMENT OF THE CLINICAL CENTERS

14.2.1 Performance Reports

Performance of the Clinical Centers with respect to case and control recruitment is assessed in weekly reports. These reports include the number of cases and controls enrolled to date and ratio of the number enrolled to the number who should have been enrolled to date given the scheduled recruitment period already completed. Each matched control should be recruited into the study shortly after the corresponding case. In addition, the CCC staff provide information about the number of women and minority cases being recruited into the study in monthly reports. Performance in other areas is assessed by consideration of the following at quarterly intervals.

1. For enrolled cases and matched controls, the number of study forms which are past due at the Clinical Coordinating Center, based on each case's date of enrollment.
2. Specimens which are past due at the core facilities.
3. Studies (e.g., pulmonary function tests or chest X-rays) which are called for by Protocol but were not performed.
4. Time between enrollment of case and enrollment of matched control.
5. Number of Protocol violations.
6. Number of forms that passed the first edit and number of forms passing the current edit.
7. Percentage of cases enrolled in Clinical Course Study with missed telephone contacts and percentage of cases who are inactive, i.e., are no longer willing or able to have the two-year examination.

The CCC staff compares performance and quality of submitted material among Clinical Centers; the areas considered include number of forms past due, studies not performed, or specimens improperly prepared or improperly labeled, etc. The CCC staff also compare each Clinical Center's quarterly performance to its own past performance and to agreed upon study standards, in order to determine whether the Clinical Center's performance is outside study standards or whether the level of performance has worsened substantially compared to its previous record. Study standards are set by weighing how crucial an item is to the study Protocol and the levels of performance which past experience has shown to be attainable.

In addition to the above analyses, performance reports include summary statistics for each Clinical Center. Large changes in these statistics from period-to-period within a Clinical Center may indicate changes in the way data are being collected. Comparison of these statistics across Clinical Centers could suggest either differences in how data are collected or differences in the patient population, and may prompt further investigation.

14.2.2 Re-Abstraction of Selected Data for ACCESS Cases and Control

For selected cases and controls participating in the etiology study, CCC staff identify tape recordings that will be used for re-abstraction of the case's or control's interview data and the form to assess quality of data entry. The tape and copies of study forms for each case or control are sent to the CCC for review and comparison with the study forms and the data entered in the computer database. Clinical Coordinating Center staff listen to the tape to ascertain whether the interviewer adhered to study procedures in conducting the interview and complete a form to record this assessment. Specifically the reviewer determines whether the interviewer followed the ACCESS script for the interview, and provided good anchors for the time frames (e.g., listing significant events occurring during the reference period) being used in the interview and for the events being collected (e.g., providing a good lay description of sarcoidosis). While listening to the tape the reviewers confirm the responses of the case or control were recorded correctly for a sample of items on the forms and that the responses match the data entered in the computer database and printed for the reviewer to check against. Beginning in 1998, the Principal Investigators of the Clinical Centers are requested to listen to the tape of one case and one control each quarter following the same procedures outlined above.

A sample of the study forms from each Clinical Center are entered into the central database by Clinical Coordinating Center staff. Beginning January 1998 specific forms are requested on a regular schedule for this quality control program. The Clinical Center data file is compared to the CCC file, and the number of errors is tabulated by whether the error was made by Clinical Center staff or CCC staff. Systematic errors are bought to the attention of the staff making these errors. A summary of these comparisons is included in the Quarterly Performance Report.

14.2.3 Site Visits

In addition to preparing the Clinical Center performance monitoring reports, the CCC staff insure data quality by conducting periodic site visits or audit visits to the Clinical Centers. Tape recordings of two cases and two controls (selected in advance by CCC staff) are reviewed in the

same way as described in Section 14.2.2. The data on the records for these cases and controls are compared against listings of data residing on the main database at the CCC as of the date of the request for a site visit. Using the data as of the site visit request should prevent any audit-prompted revisions of the data form(s). Spirometry tracings, chest X-ray reports, and pathology reports for cases are reviewed by the site visit team. Consent forms and the Laboratory Forms (Form 10) are reviewed for both cases and controls. Plans for site visits and site visit requests are provided to the Study Chairperson and NHLBI Project Office on a schedule agreed to with the NHLBI Project Office. Site visit reports summarize the findings of the site visit and are sent to the Study Chairman, Clinical Center Principal Investigator, the NHLBI Project Officer and members of the Data and Safety Monitoring Board. Recertification of Clinical Center personnel responsible for key areas of data collection may also be necessary during site visits.

14.2.4 Quality Control for Chest X-rays

A chest X-ray for each case is obtained for ACCESS. These X-rays are read by Clinical Center ACCESS physicians. A sample of ACCESS X-rays is selected and submitted to a panel of ACCESS physicians for independent assessment during the Steering Committee meetings. The repeat classifications are compared to the original classifications. Discrepancies between the two readings are summarized using the kappa statistic.

14.2.5 Quality Control for Pathology Slides

A 10% random sample of pathology slides obtained in ACCESS is collected at the CCC and sent to other ACCESS pathologists for interpretation. The two interpretations are compared using the kappa statistic.

14.2.6 Monitoring Data Quality of Spirometry and Biological Specimen Analysis at the Clinical Centers and the Core Facilities

Two methods are used to monitor the reliability of test results from the Clinical Centers and the core facilities: 1) examination of means or frequencies of key variables (e.g., results of assays) over time using control charts; and 2) duplicate interpretation of study materials. Monitoring means and

frequencies of key variables with control charts allows CCC staff to determine if and when these distributions change. Since routine changes are unexpected, an investigation is undertaken to determine whether the shift represents a change in reporting by the Clinical Center or core facility or a change in the population being studied. Results from the duplicate sample submissions are compared to assess reliability: using Kappa statistics for categorical data, Spearman's rank order correlation coefficients for ordinal data, and Spearman or Pearson correlation coefficients for continuous data. In addition, the intra-class correlation coefficients are calculated for continuous or ordinal measures.

For spirometry measures, tracings for a random sample of procedures are sent to the Study Chairman to determine whether the tracings are acceptable. For biological specimen analysis, a random sample of biological specimens is requested by the CCC staff for duplicate evaluation. The duplicate is marked in such a way that the pathologist can not determine that this specimen is part of the quality control program. The results of the two duplicate tests are compared.

Results of some tests to be performed in ACCESS can vary widely under different testing conditions. For example, it has been suggested that polymerase chain reaction (PCR) technology can detect viral DNA or RNA at concentrations as low as one sequence per 10,000 cells (Busch et al, 1992). Such high levels of sensitivity require that the PCR tests are performed under exacting conditions with no possibility of contamination (Bitsch et al, 1992). The conditions for these sensitive assays are stated in Volume IV of the Procedures Manual.

14.3 QUALITY ASSESSMENT OF THE CENTRAL REPOSITORY

14.3.1 Introduction

A Central Repository is responsible for storing blood and other specimens, as required by the Protocol. This study requires careful storage of these specimens for future analyses. The CCC staff prepares quarterly reports showing the performance of the Central Repository in storing the laboratory specimens.

14.3.2 Monitoring the Flow of Data

Specimens are sent directly to the Central Repository or a designated core facility from the Clinical Centers; the specimen transmittal forms are data entered in the Clinical Center. CCC staff create an electronic log of all specimens sent to the Central Repository from these forms. It is the responsibility of the Central Repository staff to complete a report about the condition of each specimen received, (e.g., frozen or thawed), and the number of aliquots received for each specimen number. The Clinical Center log is used to identify as delinquent any reports not received from the Central Repository within the time allotted after the Clinical Centers have shipped the specimen. Central Repository reports are considered delinquent if they are not received within two weeks of the date the Clinical Center sent in the specimen. CCC staff prepare quarterly reports on data delinquent from the repository, and whether the proportion of delinquencies exceed agreed upon tolerance limits.

14.4 QUALITY ASSESSMENT OF THE CLINICAL COORDINATING CENTER

During site visits to the Clinical Coordinating Center, CCC schedules are reviewed to determine the timeliness of the data acquisition from the Clinical Centers and the core facilities. Site visitors insure that the data being collected at the CCC are secure, and that patient identifiers are removed to prevent linking study materials to an individual except by his/her study number. The reviewers monitor the progress of the Random Digit Dialing Interview Group in identifying the RDD controls for the etiology study.

There are certain activities CCC staff carry out to insure the quality of the data and analyses.

1. Persons (such as the Principal Investigator and Co-Investigator) not involved in the development of the data editing programs fill out a few study data forms, making deliberate errors. These forms are keyed and processed through the data editing system to see if all of the errors are detected by the data management system.

2. A sample of original data forms are compared against the data on the CCC computer (as part of re-abstraction procedures and the site visit procedures described in Sections 14.2.2 and 14.2.3). This procedure is used not only to detect data entry errors, but also to detect problems with the editing software developed and implemented by the Clinical Coordinating Center.

3. For each continuous variable on the database, a point frequency distribution (i.e., a tabulation of the frequency of occurrence of every distinct value) is obtained. This helps to identify many types of abnormalities in the continuous data such as: (a) digit preferences; (b) biomodality or other distinctive shapes of the distribution; and (c) outliers (i.e., extreme values distinctly separate from the rest of the distribution).

   Once an observation has been identified as a true outlier, the first step is to go back to the original records and determine whether a recording or keying error was made. If such a value has been verified as correct through the distributed data system, an inquiry is made as to the reasons an outlier exists. The question of whether or not to include the value in the data analysis depends upon the nature of the analysis. There is no reason to exclude the value if the analysis is a count of the number of participants having a value exceeding a given cut-point. However, if measures of central tendency and variability are being computed, or if correlation or regression analyses are being carried out, non-parametric statistics may be preferable.

4. New analysis programs (including those that utilize standard statistical packages such as SAS) are tested by running these programs on a small subfile of 10 or 20 participants and independently reproducing the tabulations and statistical calculations from the original data. These procedures help to assure that the correct variables have been selected from the analysis file, the variables and cut-points have been defined properly, and that transformations of the original variables on the analysis file have been formulated correctly.

5. When preparing data reports, different tables, which may have resulted from a variety of analysis programs, are checked for consistency of denominators.

CHAPTER 15

DATA MANAGEMENT SYSTEM

15.1 OVERVIEW

The Clinical Coordinating Center data management staff designed and implemented the distributed data management system (described in Chapter 11) to be used in the Clinical Centers as well as the data management system for the Clinical Coordinating Center. The Clinical Center staff have responsibility for data entry (and correction if necessary) of all case and control study forms and for transmitting the data to the Clinical Coordinating Center on a regular schedule. Clinical Center staff use a central automated telephone response system (ATRS) to register cases and controls. Data from laboratories are transmitted electronically to the Clinical Coordinating Center. The Clinical Coordinating Center staff have responsibility for editing, storing and analyzing all received study data. Clinical Coordinating Center staff use microcomputers and a central workstation on a local area network.

15.2 DATA MANAGEMENT STAFF

Clinical Coordinating Center staff collaborate with Clinical Center staff in the operation of a distributed data management system dedicated to ACCESS. Designated Clinical Coordinating Center staff interact with Clinical Center staff to maintain the operations of the distributed system. Since the Clinical Coordinating Center have microcomputers identical to the Clinical Center's machine, the Clinical Coordinating Center staff are able to "walk through" Clinical Center problems. In the event Clinical Center staff report a hardware failure (e.g., damage to a hard drive), steps are taken immediately to provide a loaner machine and replace the damaged hardware to avoid interruption to Clinical Center activities. A software package allowing remote access to the microcomputers in the Clinical Center is used by Clinical Coordinating Center staff for resolution of problems.

15.3 FORM EDITING

Forms are edited for legal codes, valid ranges and logical consistency by electronic checks during data entry and immediately after completion of data entry at the Clinical Center. A form is available for transmission to the Clinical Coordinating Center after data entry. Forms are transmitted to the Clinical Coordinating Center on a regular schedule. Once the form is received in the Clinical Coordinating Center, the data are edited more extensively.

Study data are edited in the Clinical Coordinating Center for completeness, internal consistency, consistency with previous data from the same patient, and numerical values outside of specified limits. Edit queries for a given form are printed and sent to the appropriate Clinical Center. Clinical Center staff correct forms using screen images of the data form. All corrections made are electronically audited. The audit file includes the old and new values for the field, date of the correction and who made the correction. The form is automatically marked as corrected once responses to edits have been made and accepted.

15.4 PROTOCOL ADHERENCE AIDS FROM DATA MANAGEMENT SYSTEM

The Clinical Coordinating Center staff prepare and distribute protocol adherence aids using the central data management system. These protocol adherence aids include lists of cases and controls enrolled in the study and lists of biological specimens submitted to all laboratories and the Central Repository.

Labels for biological specimens, correspondence and form pages are printed at the Clinical Coordinating Center and mailed to the Clinical Centers. Software to assist in scheduling case and control appointments is available on the Clinical Center system.

An inventory of all forms entered for each patient is available on the Clinical Center microcomputer as a screen or print-out on demand. Other computer programs which the Clinical Center staff require to meet the objectives of ACCESS are developed as needed.

15.5 DATA EXTRACTION FOR ANALYSES RELATED TO RESEARCH OBJECTIVES

The Clinical Coordinating Center database is the archive for all data from the Clinical Centers. Once every week, Clinical Coordinating Center staff link with the computer at the Clinical Center to transfer the data entered in the previous week. Clinical Coordinating Center staff transmit summary data, reports and software releases as needed. The content of semiannual data reports is defined and appropriate data extracted from the main database to prepare these reports. Preparation of an analysis file from the database creates a file with contents that do not change as the database is updated and prevents an inadvertent alteration of the database while running analysis programs.

15.6 DATA BACKUP

The Clinical Coordinating Center staff utilize a variety of safeguards to protect the study from catastrophic loss of data. There is routine backup of all ACCESS files in the Clinical Center. In the Clinical Coordinating Center, the databases are archived on a daily basis. Other files including programs used for all data management functions are fully archived once every week with an "incremental" backup daily. An incremental backup is one in which only files that have been modified are archived. The back-up system is designed to permit the recreation of the system with a minimum expenditure of time and money should any file be destroyed. Prior to any major change in the operating system, back-up tapes of the main database are created and saved for a minimum of six months.

Analysis files extracted from the database for the purpose of generating the periodic data reports are copied onto magnetic tapes and stored for at least two report periods off site and/or at the Clinical Coordinating Center. Back-up copies of analysis files and programs used in the preparation of scientific presentations and publications are retained for the duration of the contract and stored off site. The back-up copies of the analysis files include the programs and procedures that are utilized to extract the data from the database. Clinical Coordinating Center staff provide a computer program on the distributed data management system for routine use by Clinical Center staff to locally archive the database and programs and copy them to tape.

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