Report of the Workgroup on Therapeutics

Background and Progress Since Coolfont

The primary goal of AIDS therapeutics research is to find treatments to reduce death and suffering among persons infected with the HIV. The Federal Government, the pharmaceutical industry, and university-based laboratories and clinics are collaborating in a major national effort to discover, develop, and evaluate new therapies for HIV infection. Collectively, these initiatives form a national commitment to HIV therapeutics research.

Substantial progress has been made in this effort. One drug, AZT, has been shown to prolong survival in certain groups of patients with clinical AIDS and AIDS-related complex or ARC. (Although the designation "AIDS-related complex" is being phased out in surveillance and other studies, it is still widely used in clinical practice.) The benefit of AZT was demonstrated in a randomized trial, and the drug was approved in 1987 by the Food and Drug Administration (FDA) for treatment of patients with severe HIV infection, as evidenced by certain clinical or laboratory signs of substantial immunologic compromise.

The interval from the discovery of AZT's anti-HIV properties *in vitro* to its approval by FDA for general medical use was approximately 2 years--an exceedingly short time for such an accomplishment. This was made possible by effective collaboration between the Burroughs Wellcome Company and the Public Health Service (PHS).

Several other drugs are in early phases of testing in HIV- infected persons. Still more are in preclinical evaluation, and several of these will likely be in clinical trials within a year or two. Studies are also in progress to evaluate therapies for the full range of problems faced by HIV-infected patients, including opportunistic infections and malignancies. In addition, a program of trials directed at HIV-infected children has been created.

The most important goals of clinical trials are to find drugs that are effective and to eliminate those that are not, or that are unsafe. This requires an orderly process of trials that are well designed and conducted in a manner that will ensure the reliability of the results. At the same time, it is important to recognize the desire of patients to have access to experimental drugs, particularly since such access provides hope to individuals with a still fatal disease.

It is essential that both of these goals be met. This can best be accomplished by first testing new drugs in rigorous clinical trials, then making those drugs that show evidence of safety and efficacy available to large numbers of patients through the recently revised treatment IND (investigational new drug) mechanisms. It is also important to ensure equal access to experimental treatments for all affected populations. The treatment IND allows such access.

Ultimately, success in treating HIV infection will depend on successful research, both basic and applied. While no one can predict with certainty an outcome that rides on the ability to make new discoveries, there is substantial reason for optimism. Evidence gathered by the scientific community strongly supports the view that HIV can be suppressed by drugs or biologic agents. Most importantly, one drug has been found and made widely available. In addition, much has been learned about the basic mechanisms of the life cycle of the virus. Such progress in basic HIV-related research forms the basis for applied research. In the area of applied research, programs under way are seeking drugs to attack HIV at each step of the replicative process.

Another promising area for therapeutics research involves modifying the response of the host to the virus. The development of biological response modifiers, or immunomodulators, will be solidly based on an increasing understanding of the pathogenesis of HIV-related disease. Knowledge of how host tissues respond to HIV infection can lead to therapies that attack the virus or restore the function of the immune system.

Both the public and private sectors have been very active in preclinical developmental therapeutics. PHS has established a coordinated drug discovery and development rationale that includes the following elements:

- ***Acquisition of synthetic compounds and natural products and their screening for anti-HIV activity.*** A program has been established to acquire natural products and synthetic compounds and to test them in the laboratory for activity against HIV. A centralized screening facility tests, in a standardized assay, different structural entities to determine if they can inhibit HIV replication *in vitro*. Promising compounds identified in the PHS screening program, or in screening programs operated by others, can be developed by PHS right up to, and into, clinical trial. The aim of this program is to facilitate the development of new therapies and

to move the development process quickly to the private sector.

Investigator-initiated grants have been awarded to encourage innovations in the development of therapies for HIV infection and of new methods to test and screen new compounds against HIV.

- ***Targeted drug discovery.*** A program has been initiated to facilitate the rational development of therapies aimed at specific molecular targets. Because such an effort requires expertise from a number of scientific disciplines that are rarely found within a single institution, the National Cooperative Drug Discovery Groups have been established. Each group (there are approximately 22), focusing on a specific molecular target, brings together scientists from multiple institutions who work cooperatively to discover and develop drugs for the selected target. Most of these groups are linked with a pharmaceutical firm so that any drugs discovered can move rapidly into development and application. The program has already led to discovery of four specific drugs that should be entering clinical trials in the next 12 to 18 months.

- ***A national repository for research reagents.*** The repository will serve as a clearinghouse for information on reagent availability. It will distribute, to the scientific community, key research reagents, including infectious clones of HIV, different strains of HIV, monoclonal and polyclonal antibodies, cell lines for growing the virus, subclones that express soluble proteins, and standardized biochemical antiretroviral screens that can be used to assay compounds for potential antiviral activity.

The pharmaceutical industry has played an active role in HIV drug development. According to the Pharmaceutical Manufacturers Association, as of August, 1988 at least 56 firms have more than 43 drugs in the IND phase, including 15 antivirals, 22 immunomodulators, and 6 anti-infectives.

A coordinated program for clinical trials has been established by PHS. Under this program, the AIDS Clinical Trials Group--a cooperative group of 35 institutions funded by PHS to evaluate therapies for AIDS--works continuously to develop and carry out multidisciplinary clinical trials of the highest priority. The group is studying treatments for HIV infection, opportunistic infections, HIV-related malignancies, pediatric HIV infection, biologic response modifiers, and the pharmacology of new drugs.

The Clinical Trials Program is a national resource for evaluating AIDS therapies. Collaboration with the pharmaceutical industry is an essential ingredient of this effort. Indeed, most of the drugs under study in the program are the result of joint efforts with the pharmaceutical industry.

The Clinical Trials Program has many accomplishments to its credit:

- Clinical trials have been initiated with drugs or biologics that target each aspect of the HIV syndrome, the primary infection as well as complicating infections. Treatments are being tested for each of the major opportunistic infections, including *Pneumocystis carinii* pneumonia, cytomegalovirus infections, and toxoplasmosis. In addition, several immunomodulators are under study;

- Clinical trials of AZT have been initiated for asymptomatic HIV-infected patients. A separate trial in asymptomatic HIV-infected hemophiliacs is also in progress;

- A concerted program of clinical trials in children is in progress. A phase 1 trial of AZT has been completed in this population;

- Several clinical trials are under way to test for effective therapies for Kaposi's sarcoma and lymphoma;

- A formal mechanism has been established to select drugs for clinical study in NIH-supported trials;

- The early availability of drugs that show evidence of safety and efficacy has been addressed. Treatment INDs have been approved by FDA for AZT and trimetrexate; and,

- FDA has streamlined its procedures to ensure speedy review of investigational new drugs and new applications related to HIV infection.

Issues, Goals, and Objectives

AIDS therapeutic efforts are directed toward a number of achievable and interrelated goals. Broadly stated, these are:

- to decrease or prevent death and suffering in patients with HIV infection;

- to decrease or prevent progression from the asymptomatic seropositive state to overt illness;

- to decrease or prevent the occurrence and severity of opportunistic infections;
- to decrease or prevent the occurrence of HIV-related cancers (secondary to the immunosuppressed state);
- to decrease or prevent new HIV infection; and,
- to decrease the infectivity of people who carry HIV.

To accomplish these broad goals, seven areas will need increased attention: (1) preclinical drug discovery and development; (2) private sector efforts to develop therapies for HIV infection; (3) clinical trials, using rigorous scientific methodology to ensure rapid and reliable results; (4) equal access to clinical trials for all HIV-infected populations; (5) effective communications to inform the research community, the HIV-infected population, and the public about clinical trials and research findings; (6) training of professionals for clinical trials research, and, (7) rapid availability of safe and effective therapies, once identified, to all patients.

The prospects for developing effective new therapies are promising, since the talents of many excellent scientists are now engaged in this research. The greatest likelihood of success lies in the simultaneous efforts of many laboratories.

Nevertheless, much remains to be done. The history of drug development suggests that only 1 of every 10 to 20 drugs entered into human trials will eventually be found to be effective and safe. Despite this, if the scientific methodology for the design and conduct of clinical trials is allowed to prevail, it is likely that a significant number of therapeutic agents will be available within the next 5 years. These agents can be expected to make a major impact on AIDS in this country.

Issue: Regulation of New Therapeutic Products

Goal: Accelerate FDA review of new therapeutic products for AIDS by implementing the Vice President's directive on expedited approvals.

Objectives:

- Facilitate agency consultation with the sponsor before phase 1 testing begins to help identify necessary animal studies, thereby reducing the time required to begin clinical trials of promising safe drugs.
- Facilitate early consultation by the agency with the sponsor to develop phase 2 studies that could provide definitive data on safety and effectiveness warranting market approval.
- Enhance focused FDA regulatory research on critical rate-limiting aspects of the preclinical, clinical/manufacturing, and clinical phases of drug development and evaluation.
- Utilize risk-benefit analyses for new AIDS therapies that balance the risks of the disease against the identified benefits and risks of the product.
- Increase use of the treatment IND as a bridge between completion of phase 2 testing and final marketing approval, including actively working with the sponsor to evaluate the appropriateness of assigning treatment IND status to specific therapies while phase 2 data are being analyzed and assembled.
- When appropriate, request phase 4 (post-marketing) studies following approval of AIDS products, to develop additional information about the products' risks and benefits.
- Actively monitor the conduct and evaluation of clinical trials to assure that clinical trials and product reviews are proceeding on schedule. Develop or augment, as appropriate, clearinghouse mechanisms for informing physicians and patients of investigational therapies for AIDS.
- Implement necessary safeguards to assure patient safety and the quality of clinical trials.
- Perform Good Manufacturing Practices (GMP) inspections earlier in the clinical investigational (IND) stages to ensure that the drugs tested will meet the requirements for FDA evaluations at the new drug application (NDA) or licensing stage.

Goal: Develop an adequate scientific base in FDA to support the regulatory mission of product evaluation and post-marketing surveillance of AIDS therapeutics.

Objectives:

- Enhance current and develop additional mechanisms to assure FDA's access to scientific information and advice from the scientific community and the agency's other constituencies.

- Develop a plan for a training grants program in which educational loans can be repaid through FDA service.

- Develop programs to enhance the recruitment and retention of FDA researcher/reviewers.

- Enhance current mechanisms to assure that FDA has adequate facilities and equipment to support the addition of new researcher/ reviewers.

Issue: Preclinical Drug Discovery and Development

The overall goal of preclinical therapeutics is to discover and develop new compounds to treat HIV infection and its sequelae, including opportunistic infections. As already described, an extensive array of efforts has been launched by PHS and the private sector to address this goal.

Both the public and the private sector face a variety of difficulties, in all phases of drug development, that have a negative impact on bringing new therapies into clinical trial. PHS can help investigators through the drug development process.

Goal: Continue to support the AIDS drug development program of the NIH, including all phases of drug discovery and development, during the next 5 years.

Objective:

- Provide adequate resources to allow a five year commitment for coordinated programs within NIH to pursue the discovery and development of new therapies for HIV infection.

Goal: Continue extensive *in vitro* screening of natural products and synthetic compounds at the current capacity of approximately 20,000 compounds per year.

Objective:

- Increase efforts to acquire and test compounds from academic and private sources. Notify these sources of the availability of this centralized testing service.

Goal: Examine biochemical and molecular targets unique to HIV for potential drug design and development.

Objective:

- Expand the NIH drug development programs to foster multi-institutional and multidisciplinary research and to maximize investigations of the molecular biology and the biophysical properties of HIV and host cell proteins important in the replication of the virus.

Goal: Evaluate animal models for retroviral therapy for their possible usefulness in predicting or optimizing effective therapies for HIV infection.

Objectives:

- Expand the NIH animal models program, using known animal retroviruses that infect murines, felines, and primates.

- Provide resources to acquire or scale up and test additional compounds from academic and private sources.

- Develop other, more novel animal model systems that could be used in the development of therapies.

- Expand research on the development and use of transgenic animals that express HIV proteins, in order to determine the effectiveness of drugs in inhibiting specific viral functions in animals.

- Expand efforts to identify animal models that can be used in developing drugs to treat the opportunistic infections associated with HIV infection.

Goal: To optimize therapies for study in man, stimulate research and provide resources to evaluate synergistic or antagonistic interactions of test combinations of anti-HIV therapies *in vitro* and *in vivo*.

Objectives:

- Optimize combination therapies by providing the resources to test and analyze these therapies *in vitro* and *in vivo*.

- Provide resources to encourage investigator- initiated research on the molecular mechanisms of synergy or antagonism.

- Provide a centralized resource to test possible combinations of drugs *in vitro*.

- Provide animal model resources to determine initial interactions of combinations and to optimize the best combinations identified in clinical trials.

Goal: Initiate additional studies of the mechanisms of action, metabolism, and other aspects of the cellular pharmacology of anti-HIV therapies.

Objectives:

- Explore alterations in tissue distribution, cellular uptake, and patterns of activation and metabolism of antivirals, as well as resulting levels of toxicity.

- Explore the effect of cytokines on HIV-infected and noninfected cells. Cytokines can act on the long terminal repeat (LTR) sequences of HIV genes, resulting in activation of the proviral genome and production and release of infectious virions. Better understanding of the molecular mechanisms underlying this activation process, and the biological consequences of such activation, is needed to develop more effective and noncytotoxic therapies.

Goal: As part of the NIH AIDS drug development program, establish systems for discovering and developing therapies for the major opportunistic infections associated with AIDS.

Objectives:

- Establish a program to foster basic research aimed at rational drug design and discovery of new therapies to treat opportunistic infections.

- Initiate NIH programs to establish multi- disciplinary, multi-institutional research groups for the treatment of these opportunistic infections.

- Encourage efforts to expand research on all phases of rational or targeted drug design. Knowledge of the molecular biology and the structural and biophysical properties of the opportunistic organisms, as well as biochemistry, genetics, and pathogenesis is needed.

- Expand and develop *in vitro* and *in vivo* systems to determine the potential of new therapies for mycobacteria, toxoplasma, candida, pneumocystis, cytomegalovirus, Epstein-Barr virus, and other opportunistic infections associated with HIV infection, administered alone or in combination with anti-HIV drugs.

- Provide resources to augment the drug development efforts of the public and the private sectors to ensure that effective therapies reach clinical use as rapidly as possible.

Goal: Institute new initiatives to discover drugs effective in eradicating latent or persistent HIV infection.

Objectives:

- Encourage research into the mechanism of viral integration and activation from the latent state.

- Develop methods to screen drugs that induce or suppress latency *in vitro*, and/or block incorporation of the viral genome into cells.

- Explore host factors involved in formation of proviral DNA.

- The simian immunodeficiency virus (SIV) model may be invaluable for identifying host-related factors required for establishment of a latent infection. SIV, the simian analogue of HIV, acts in two drastically different ways in two simian species, giving rise to productive infection in one host and latent infection in the other. The SIV model thus offers an ideal system for studying latency as it relates to host-specific factors, and identifying potential targets for drugs designed to prevent virus activation or to extend the latent stage.

Goal: In consultation with extramural experts, develop and promulgate minimum guidelines for establishing the activity of candidate drugs in preclinical systems.

Objective:

- Meet with extramural experts to determine the type of information to be provided in the minimum guidelines, and the groups to be informed.

Issue: Private Sector Participation

The private sector should participate fully in the research and development of therapies for patients with HIV infection. Private industry has in progress many initiatives in HIV therapeutics, but additional measures can be taken to stimulate further efforts.

Goal: Reduce barriers to the commitment of private industry resources and create incentives for such commitment.

Objective:

- Convene a joint PHS-industry workshop that will identify ways to increase the commitment of private industry to the research and development of therapy for patients with HIV infection. Examples of topics that should be discussed at such a workshop include interchange of scientific information; availability of reagents and

methods; liability concerns and ways to alleviate them; tax incentives, marketing exclusivity, and patent term restoration provisions available under current laws; and the possibility of developing additional incentives through legislation.

Issue: Rapid Development of New Clinical Protocols

Rapid development of clinical protocols is extremely important to the identification and appropriate use of new therapies. "Windows of opportunity" for the execution of well-designed trials are frequently short, and end once access to new, adequately tested agents becomes widespread.

Goal: Reduce obstacles to the rapid development of new protocols.

Objectives:

- Provide adequate training for staff developing protocols.
- Develop a system for rapid communication among relevant participants, including principal investigators, NIH staff, industrial sponsors, and the FDA.
- Facilitate rapid access to protocols already developed and to reviews of the most recent data on the specific manifestation or stage of disease under study.
- Periodically assess and prioritize broad therapeutic areas in HIV infection most in need of development of new drugs.
- Review current institutional review board (IRB) procedures to ensure maximal speed and flexibility for the testing of experimental therapies.

Issue: Ensuring Valid Results of Clinical Trials

Because an overwhelming urgency surrounds the development of therapeutic interventions for HIV infection, the collection of accurate and reliable data that can be evaluated rapidly is of even greater concern than in most other types of clinical trials. The results of efficacy trials must be valid and free of bias. An effective data-collection effort will also reduce the need to replicate studies with ambiguous results or with results that are clear but of poor quality.

Goal: Data collected in clinical trials should be validated and verified to ensure that conclusions drawn represent an accurate assessment of the intervention.

Objectives:

- Stimulate the use of Data and Safety Monitoring Boards to guarantee appropriate interim evaluation of safety and efficacy data collected in the course of pivotal efficacy studies.
- To enhance compliance and the timely completion of studies, clearly communicate the separate responsibilities of trial sponsors, clinical investigators, and patients in the clinical trial process.
- Establish procedures to ensure quality control and quality assurance of data throughout the course of clinical evaluation.

Issue: Research and Information Exchange

Efforts to develop new therapies for HIV infection are taking place in unique circumstances that have an impact on clinical trial methodology. Factors include the perspectives of practitioners, investigators, and patients on treatment of an infection that produces a life-threatening disease; the use of unproved therapies; high dropout rates from clinical studies; and misinformation from a variety of sources.

Interest has increased in exploring a variety of alternative strategies for evaluating new therapies for HIV-infected patients. Randomized, controlled clinical trials have been the most reliable and efficient means of obtaining the needed safety and efficacy data. However, the special circumstances surrounding HIV drug development have raised the possibility of modifying clinical trial methodology in a number of ways--for example, in choice of control groups for different disease subgroups, choice of appropriate endpoints, and the type of evidence needed to support the use of measures of efficacy other than mortality. To address these emerging issues, greater communication is needed among government, industry, and academic researchers and private practitioners. There is also a need to make the public, investigators, and study planners aware of how clinical trials must be designed, implemented, and monitored to ensure that the resulting evidence is reliable and can support expedited availability of therapies to affected patients.

Goal: Coordinate and foster increased participation among government, industry, academic scientific investigators and private practitioners in the evaluation and development of appropriate clinical trial designs and practices.

Objectives:

- Conduct public workshops on clinical trial design.
- Enhance monitoring and analysis of existing clinical trials.

Goal: Develop mechanisms to facilitate timely information exchange among the public, Government, industry, academia, and private practitioners regarding drug development strategies and the design and conduct of clinical trials.

Objectives:

- Provide protocol advice and feedback to industry, clinical investigators, and other appropriate parties.
- Provide guidance on the drug development process, including regulatory requirements for drug approval and the role of clinical trials.
- Educate the public about the role of clinical trials in HIV drug development.
- To the extent possible, publicize trial methodology that has or has not been successful.

Goal: Facilitate international collaboration on AIDS, especially in clinical trials for therapeutics.

Issue: Industry Access to Clinical Trials

Since the NIH's AIDS Clinical Trials Program funds a large proportion of the clinical investigators of HIV therapies in the United States, it represents a practical resource for the testing of new drugs. It is critical that the pharmaceutical industry have effective access to this resource. There must be a clear perception by industry that its participation is welcomed, that there is an effective means of prioritizing the use of these resources, that the data collected will be reliable, and that collaborating firms will have full access to the data. In return, the collaborating firms must cooperate fully with PHS and the clinical investigators.

Goal: Ensure full opportunity for access to this system by pharmaceutical sponsors who wish to have their drugs tested by NIH's AIDS Clinical Trials Group.

Issue: Targeting Central Nervous System Disease

Both adults and children with HIV infection may have prominent neurological damage. Antiretroviral (HIV) therapy is likely to benefit these patients.

Goal: Develop drugs specifically targeted to central nervous system disease. Perform quantitative evaluations of psychiatric changes in patients entered into clinical trials.

Objectives:

- Provide adequate facilities and trained personnel to perform these evaluations.
- Develop therapeutic protocols aimed at identifying patients with very early HIV-related dementias and determining the effects of experimental therapies in this population.

Issue: Preventing Infection of Persons at Risk

HIV infection must be prevented in persons at high risk of exposure. Such individuals include children of infected mothers, spouses/sexual partners of high-risk individuals, health care personnel, and laboratory workers accidentally exposed to HIV.

Goal: Identify and test drugs that can prevent infection among persons exposed to HIV or at high risk for such exposure.

Objectives:

- Study the prevention of transmission from infected persons on anti-HIV drugs to their sexual partners or their offspring.
- Establish animal models to test drugs as chemoprophylactic agents.
- Conduct studies of drugs for postexposure prophylaxis among persons accidentally exposed to HIV.

Issue: Role of Community Care Providers in Clinical Research

Community medical care providers are enthusiastic about the prospect of becoming more involved in medical research into HIV infection. This is important for a variety of reasons. Community providers care for most HIV-infected patients, including the vast majority with asymptomatic infection. Moreover, patients cared for in the community setting are using a variety of treatments; systematically collected data on the results of these treatments could disclose useful leads for further study. Finally, the true import of research advances can be measured only by understanding

their application in typical clinical community settings.

Goal: Develop programs involving community providers and their patients in clinical research appropriate to, and best conducted in, the community setting. Conduct research on patterns of care and the disease's natural history, the systematic surveillance of commonly used but untested therapies, reporting evidence of their safety and/or efficacy.

Objectives:

- Convene a meeting to discuss with community medical care providers their interests and their needs for participation in clinical research related to HIV infection.
- Develop models or exploratory programs addressing the goal of involving and training community care providers and their patients in clinical research.
- Evaluate these programs for their contribution to biomedical research.

Issue: Applying the Results of Clinical Research

It is not enough to discover new drugs and to perform clinical trials to evaluate their usefulness; new therapies must be rapidly applied to the care of HIV-infected patients. Increased attention must be devoted to the transfer of effective therapies and research findings from the research setting to the care of HIV-infected patients.

Goal: Use the treatment IND mechanism to make new drugs available to patients after preliminary evidence of safety and efficacy has been obtained.

Objective:

- As data become available on drugs in phase 2 and phase 3 trials, encourage sponsors to use the expanded treatment IND mechanism and, if no private sponsor is available, sponsor treatment INDs for appropriate drugs.

Goal: Involve community care providers in clinical trials.

Objective:

- Provide demonstration project funds and training to enable community care providers to participate in clinical trials.

Issue: Access to Experimental Therapies

HIV infection produces a life-threatening illness for which there is currently only one therapy (AZT) with proven efficacy. Although this drug prolongs survival, there is no evidence of a cure at present.

Access to experimental therapies gives patients a sense of hope. Participation in clinical trials often offers increased access to specialized medical care and support services. While it may not be feasible to build a clinical trials system that can accommodate all HIV-infected adults, it is especially important to structure clinical trial networks so that equal opportunity for access to clinical trials exists within all categories of patients.

Goal: Design and locate clinical trials and research centers to specifically include patients across all affected ethnic and socioeconomic strata and in reasonable proximity to where the disease is occurring.

Objectives:

- Identify barriers that reduce access of HIV-infected individuals to the clinical trials system.
- Develop strategies to remove these barriers--for example, by targeted expansion of the current clinical trials network or by providing certain social services needed by particular populations.
- Require that studies funded by PHS be designed with only scientifically driven, clearly stated exclusion criteria.
- Increase the involvement of community-based health care providers and their patients in clinical trials appropriate to the community setting.
- Develop guidelines for private trial sponsors and encourage their adherence to the standards set forth by PHS.
- Develop informed-consent procedures that are sensitive to the cultural and language needs of all populations.
- Develop a clinical trials system that addresses important questions in the treatment of all groups of patients who will use new therapies.

Issue: Ethical Issues Related to Patient Care

Goal: Identify and evaluate ethical issues related to clinical decisions in caring for patients with HIV infection, including access to health care, research protocols, prevention strategies, and availability of

experimental therapies. Expand research efforts aimed at patient choices about treatment, involvement in research protocols, and personal high-risk behaviors.

Issue: Communicating Results of Clinical Trials

Because of the extraordinarily sensitive and potentially sensational nature of any new information about the possible efficacy of new therapeutic agents for HIV infection, public announcements regarding data from clinical trials must be subject to immediate independent evaluation and scrutiny by the FDA, the scientific community, and the general public.

Goal: Ensure that, when the sponsor of a clinical trial makes claims about the therapeutic value of the substance tested, FDA has discretional authority to release as much information as necessary for the public to weigh and consider the significance of the claims.

Objective:

- Review current regulations and statutes that bear on such FDA release of information.

Issue: Communication and Education Programs

For therapeutic trials to be successfully developed and completed, better communications and education programs are needed. PHS and its component agencies should amplify their communications and education programs dealing with new drug development and therapeutic trials.

Goal: Ensure maximum communication with the public.

Objective:

- Provide accurate and timely information about new developments in AIDS therapeutics research, including realistic timetables for progress and explanations of the way drugs progress from test tube to human use.

Goal: Ensure maximum communication with patients and their families.

Objective:

- Provide specific facts about clinical trials of new therapies as well as facts about available therapies. Include telephone hotline services that can direct patients who wish to volunteer for new experimental trials to appropriate centers for evaluation. Pay particular attention to communicating the definitions and goals of preclinical phase 1, phase 2, and phase 3 testing.

Goal: Ensure maximum communication with investigators and medical care providers who see patients with AIDS.

Objective:

- Disseminate knowledge about clinical trial design and statistical methods. In cooperation with traditional professional societies (including those for doctors, nurses, and other caregivers), plan or support continuing education about new drug developments, preclinical studies, phase 1 testing, and controlled trials.

Issue: Clinical Research Training for Health Care Professionals

There is a critical shortage of certain professionals trained in clinical trial research. These include physicians, biostatisticians, experts in mechanisms of drug action, clinical trial nurses, and others. Moreover, clinical trial design and evaluation should be recognized as a valid academic discipline.

Goal: Support training programs and long-term career opportunities to enlist enough professionals to ensure proper selection of promising agents for clinical trials, an adequate understanding of the mechanisms of drug action, and the development and conduct of properly designed, well-performed clinical trials.

Objectives:

- Develop and implement interdisciplinary fellowship programs specifically dedicated to training selected health professionals in clinical research, with the specific goal of establishing training positions at NIH, FDA, and academic centers. The pharmaceutical industry should support similar training.

- Develop long-term support for clinical trial career positions in academic centers.

- Support professional associations and scientific journals in fields relating to clinical trial research and encourage PHS and industry professionals to participate in them.

AIDS in Children

The incidence of pediatric HIV infection in the United States is increasing. As of late September 1988, more than 1,100 children with AIDS have been reported to the CDC, and it is estimated that by 1991 the number will almost triple, to approximately 3,000 cases. This estimate reflects only those children with AIDS as reported to CDC; it does not include other children who are infected with HIV but who are either asymptomatic or in the earlier stage of disease called ARC. For every child who meets the definition for AIDS, at least another two or three are probably infected with the virus. It is estimated that by 1991 the number of HIV-infected children in the U.S. will reach 10,000 to 20,000.

The vast majority of children with HIV infection have acquired it from their infected mothers through perinatal transmission. Often these mothers are intravenous drug users or the sexual partners of IV drug users. They may also be poor, single, of minority origin, and involved in illegal activities (e.g., prostitution, illegal immigration, drug use). Access to health care for these children is frequently limited and may be nonexistent.

Programs for children with HIV infection must be developed with the knowledge that these children may come from families where one or both parents are also infected. Illness of the parent(s) may necessitate foster care or guardianship for the child. Special efforts should be made to develop experimental therapies and make proven treatments accessible to HIV-infected children.

Future clinical studies will also be needed to evaluate antiretroviral therapy in newborns of HIV-infected mothers as well as in asymptomatic infected infants and children. As effective therapeutic strategies are developed, their use during pregnancy and at parturition will need to be evaluated.

Issue: Getting Children into Clinical Trials

To optimize therapeutic advances for symptomatic HIV-infected children, children who meet the requirements of research protocols should (consistent with information about safety of the product) have the opportunity to be enrolled in an established clinical trial. The more patients studied, the more rapidly therapeutic efficacy of an experimental drug, or the lack thereof, can be established.

Goal: Provide children with AIDS who meet the requirements of research protocols the opportunity to participate in well-designed clinical trials.

Objectives:

- Establish, through the existing pediatric clinical trials network, a *clinically based* system to ascertain the numbers of infected, symptomatic children who may be eligible for treatment trials. This objective recognizes the fact that the CDC surveillance definition of pediatric disease may not be adequate for guiding targeted clinical activities such as treatment programs to assess efficacy and safety of new drugs.

- Evaluate periodically the efficiency and scope of the existing pediatric clinical trials network. Consider expansion of the network at such time as this may be appropriate.

- Assist other Federal agencies that have direct responsibility for providing standard care to children in the development of models of care for HIV-infected children. Relay to these agencies the knowledge and experience accrued from development of the clinical trials network--experience that may guide development of a care network that in turn will interact with the clinical trials network.

- Review the recommendations of the Secretary's Initiative on Pediatric HIV Disease and develop an implementation plan for those recommendations that relate to clinical trials and treatment initiatives.

Issue: Addressing Barriers to Pediatric Care

Vertical transmission from mother to child is the principal mode of HIV transmission in the pediatric age group. The sociodemographic group in which this primarily occurs comprises poor, minority, often single-parent families in which more than one family member may be infected. Lack of transportation and housing, as well as illegal activities of parents, may further complicate management of care for HIV-infected children and children with AIDS.

A number of bioethical, legal, and logistical issues may impede the entry of these children into clinical trials. Such barriers endanger the rapid evaluation of potentially lifesaving or life-prolonging therapies for children.

Goal: Ensure that therapeutic research is conducted in a comprehensive, multidisciplinary set-

ting where all barriers to care are assessed and effectively addressed.

Objectives:

- Within the existing pediatric trials network, ascertain the extent to which barriers limit access to therapeutic interventions. Determine to what extent the support provided serves to surmount these barriers.

- Interact with the Federal agencies responsible for providing ongoing care to HIV-infected children, to obtain information about the extent to which socioeconomic factors limit access to treatment, and interpret this information in the context of the clinical trials network. This information may assist in the development of ongoing care networks.

Goal: Identify and address barriers to entry into clinical trials.

Objectives:

- Within the existing pediatric clinical trials network, identify specific ethical, legal, and logistical impediments that deny children appropriate access to therapeutic intervention.

- In consultation with appropriate Federal and non-Federal groups (e.g., child health advocacy groups), develop effective methods for addressing these barriers. Relay to these groups the experience gained from clinical trial activities.

- When specific issues arise (e.g., the use of newborn screening programs to detect newborns at risk), convene, in an expeditious fashion, an ad hoc advisory group to assist in developing a consensus on how to address the pertinent ethical and legal issues.