

U.S. Food and Drug Administration



Deadly Diseases and People of Color: Are Clinical Trials an Option?

Symposium

October 25, 1996

**Howard University
Washington, D.C.**

Presented by:

**U.S. Food and Drug Administration
Howard University College of Medicine
Mid-Atlantic AIDS Education and Training Center
D.C. Local Performance Site at Howard University
in cooperation with
Maryland AIDS Professional Education Center
Howard University School of Continuing Education
Contract No. 277-95-2024**

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Overview

On October 25, 1996, the symposium entitled "Deadly Diseases and People of Color: Are Clinical Trials An Option?" was held at Howard University in Washington, D.C. The symposium comprised three panel sessions that addressed the benefits of and barriers to clinical trial participation by physicians and patients of color. Symposium participants learned about new treatments for hypertension, AIDS, diabetes, and prostate cancer--serious diseases that disproportionately affect communities of color. They also learned about the role of clinical trials in developing therapies for these diseases and improving access of minority populations to promising new therapies. In addition, participants reviewed the process used by the Food and Drug Administration (FDA) to evaluate new therapies for safety and efficacy and the regulatory mechanisms used to enhance patient access to promising new therapies. Participants also had an opportunity to examine the impact of managed care on the conduct of clinical trials. Finally, participants learned the extent to which Medicaid and Medicare cover investigational therapies.

Symposium faculty comprised distinguished medical research scientists from the public and private sectors, community leaders, health care providers, and representatives from FDA. (A list of symposium faculty can be found in [Appendix 1](#).)

The following summary presents key points raised in the presentations and in the discussion periods that followed each panel session.

Welcome and Opening Remarks

Celia Maxwell, M.D., F.A.C.P.

Eric Goosby, M.D

Vinod Mody, M.D.

Sharon Smith Holston

Dr. Celia Maxwell, Special Assistant for the Commissioner, Food and Drug Administration (FDA) and Assistant Professor of Medicine, Howard University Hospital, welcomed everyone and complimented symposium organizers for their hard work. Reviewing the day's agenda, she explained that the symposium was intended to explore the issues that prevent people of color from participating in clinical trials. Next, Dr. Eric Goosby, Director of the Office of HIV/AIDS Policy, Department of Health and Human Services (DHHS), conveyed greetings from the Secretary, DHHS, and revealed that the Secretary had included the symposium in her weekly report to the President. Dr. Goosby emphasized that DHHS is committed to supporting similar symposia with community leaders and members of the medical profession with the aim of increasing the availability of clinical trials in communities of color and ultimately ensuring that underserved patients are entered into a continuum of care.

During his remarks, Dr. Vinod Mody (Howard University College of Medicine) stated the importance of ensuring that underserved populations who participate in clinical trials are also able to benefit from the trial results. He commented on the timeliness of the symposium, noting "as we enter the new century we must [ensure] that people of color have access to health care and new technologies . . ."

Sharon Smith Holston (FDA) presented the agency's perspective on the importance of clinical trials. She began by stating that FDA's public health mission is to ensure that drugs and other health care products used in the United States are safe and effective for all Americans. She added that the main tool for accomplishing this is a well-conducted clinical trial, which provides the evidence of safety and effectiveness needed for approval by FDA. Clinical trials also are indispensable for pursuing the science of medicine--without them, scientific progress would be "paralyzed."

Ms. Smith Holston briefly described some of the steps taken by FDA to (1) make clinical trials a more flexible and effective instrument for the development of new therapies for serious and life-threatening illnesses, and (2) increase the access of patients to promising experimental drugs. In the mid-1970s, for example, FDA allowed beta blockers to be used for seriously ill patients who could not use other types of drugs. In the 1980s, (partially) in response to the AIDS epidemic, FDA introduced the Treatment

Investigational New Drug (IND) and "parallel track " mechanisms to enable HIV patients to receive promising new therapies that were still in development and not yet approved by FDA. Another mechanism, the Orphan Drug Act, encourages pharmaceutical companies to develop treatments for rare diseases. Recently, FDA has accelerated the availability of important new cancer therapies by approving them on the basis of surrogate endpoints.

Other steps taken by FDA include establishing the Office of AIDS and Special Health Issues and the Office of Women's Health. These offices are intended to keep the agency alert to the needs of groups with special health care problems. FDA has also responded to the needs of special populations by enhancing its regulatory requirements. For example, to increase the inclusion of women in clinical trials, FDA now requires gender analysis as part of the evidence of a drug's safety and effectiveness.

Ms. Smith Holston noted, however, that much remains to be accomplished in terms of bringing people of color into the drug development process. Today, about one-fourth of the U.S. population are people of color; by 2050, nearly half (48 percent) will be. Yet, only 5 percent of clinical trial participants are members of minority groups. She added that this situation is "unacceptable" and that FDA intends to do its share to bring about a much-needed improvement.

The issue of increasing minority participation in clinical trials is important on two levels: first, its significance for public health; second, its contribution to the Nation's commitment to the principles of equality and fairness. Indeed, the participation of people of color in clinical trials must increase rapidly "if the public health protection system, the pharmaceutical industry, and medical science are to truly serve the needs of the entire nation."

Panel: New Therapies for Diseases Affecting Communities of Color

Moderator: Celia Maxwell, M.D., F.A.C.P.

Panelists:

Hypertension--Otelio [Randall](#), M.D., F.A.C.C.

AIDS--David [Feigal](#), M.D., M.P.H.

Diabetes--Wayman [Cheatham](#), M.D.

Prostate Cancer--Judd [Moul](#), M.D., F.A.C.S.

Hypertension

Dr. Otelio Randall (Howard University College of Medicine) reviewed the different therapeutic approaches for treating hypertensive patients. Dr. Randall reported that hypertension (i.e., high blood pressure) is extremely common, affecting about 43 million Americans. Hypertension is a major risk for many conditions such as congestive heart failure, coronary artery disease, and kidney disease.

African Americans and Hypertension

African Americans are at particularly high risk for hypertension. In fact, they experience higher blood pressure levels at a younger age than any other ethnic group. This, in turn, results in higher hypertension-related morbidity and mortality rates among African Americans. Dr. Randall noted, for example, that end-stage renal disease is 4 to 18 times higher among African Americans, with prevalence rates peaking among 25- to 44-year-olds. He also observed that even though cardiovascular disease rates generally are declining (chiefly because of diuretics and other treatments), the rates are not declining as fast among African Americans as in other U.S. populations.

Clinical Trials for Hypertension Therapies

Dr. Randall then discussed clinical trials that had been conducted to develop hypertension therapies. First, he offered the following definition of a clinical trial: "The acquisition of data on a well-defined population, usually randomized to single blind, double blind, or triple blind fashion, with certain designs to determine any significant differences in the different treatment arms."

Dr. Randall emphasized the importance of having adequate representation of women and minorities in clinical trials, so that any treatment differences could be identified. He described the first clinical trial for hypertension, which demonstrated that hypertension-related mortality and morbidity could indeed be reduced among African-American patients. The trial included enough African Americans in the cohort so that trial results could be extrapolated with confidence to this population. During his presentation, Dr. Randall mentioned the African-American Study of Kidney Disease (AASK) clinical trial currently being conducted to determine if kidney disease can be prevented by reducing blood pressure. The trial is being conducted at 20 centers, including Howard University, and will enroll over 1,030 patients.

Current Treatments for Hypertension

Dr. Randall discussed the classes of drugs currently being used to treat hypertension, such as calcium channel blockers, angiotensin converting enzyme inhibitors (ACE Inhibitors or ACE-Is), AT-1 receptor blockers, angiotensin II receptor blockers, and post-alpha synaptic blockers. He reviewed data from clinical trials which demonstrate that specific classes of drugs are more effective for certain population groups, more protective of target organs, and more effective in the presence of concomitant conditions. These findings demonstrate that physicians should consider multiple factors when determining the treatment of choice for an individual patient; specifically:

- The patient's demographic profile (e.g., race/ethnicity, gender, age)
- The type of hypertension (e.g., diastolic, systolic, combined extension) and stage (e.g., I, II, III, or IV)
- The type of concomitant condition (e.g., diabetes mellitus, coronary artery disease), and
- The pharmacologic characteristics of the available therapeutics.

The physician should then "mix and match" these variables to determine the treatment strategy. Dr. Randall led symposium participants through the decisionmaking process and treatment steps for treating hypertensive patients with renal failure, congestive heart failure, and coronary heart disease. For example, diuretics are more effective than ACE-Is in treating patients with kidney disease. ACE-Is, however, are the first choice for treating hypertensive patients who have diabetes mellitus. ACE-Is are also the first choice for treating patients with congestive heart failure. But for hypertensive patients with coronary artery disease, beta blockers are the first treatment choice.

AIDS

Dr. David Feigal (FDA) discussed the evolution of current therapies for HIV infection, and he reviewed the data gleaned from clinical trials regarding the benefits and limitations of these therapies. Dr. Feigal also reviewed the role that FDA's accelerated approval mechanisms play in making promising new AIDS drugs available to patients earlier in the drug development process. To illustrate his point, throughout his presentation, Dr. Feigal showed a series of graphs that indicated which drugs were available in any given year for people with HIV. These graphs revealed that FDA's accelerated approval mechanisms enabled patients to receive promising drugs 3-5 years earlier than would be possible using conventional drug approval mechanisms.

Dr. Feigal began his presentation by noting several milestones in the development of AIDS therapies: identification of HIV virus, development of blood tests that allowed diagnosis and helped to ensure a safer blood supply, development of sensitive measurements of viral load, development of tools to monitor immune function, and understanding the methods of virus transmission (i.e., unsafe sex, contaminated needles, and mother/child transmission).

He explained that at any given time, about 250 new HIV agents are under study; the "success" rate is about one in ten. The targets of these drug development studies are: virus/cell binding mechanisms (e.g., CD4), virus genome decoding (i.e., reverse transcriptase [RT]), virus genome integration (i.e., integrase), virus protein regulation, and viral protein assembly (i.e., protease).

First Era of HIV Drug Discovery

The "first era" of HIV therapeutics to target the virus consisted of the nucleoside RT inhibitors (i.e., AZT, ddI, ddC, d4T). Clinical trials were key to discerning the benefits and drawbacks of this class of drugs. Trial results showed, for example, that AZT prevented mother/child transmission and that RT inhibitors had greater effectiveness when used in combination than when used alone. However, clinical trials also revealed the drugs' limitations. Antiviral effects were modest; it was unusual for a patient to completely suppress HIV replication. Furthermore, effectiveness was time-limited; resistance developed on average in about a year if a drug was used alone. In addition, many of nucleoside RT inhibitors had dose-limiting toxicity. For example, AZT patients often developed neutropenia; ddI patients developed pancreatitis.

Second Era of HIV Drug Discovery

Dr. Feigal discussed recent developments that have led to a "second era" of HIV drug discovery. These include more sensitive methods to assess a drug's effect on viral load, thus allowing drug resistance to be detected more easily. In addition, four new drugs have been developed: a non-nucleoside reverse transcriptase inhibitor (i.e., nevirapine), three protease inhibitors (saquinavir, ritonavir, indinavir), which, when used in combination with other therapies, can have a powerful effect on reducing viral load. The combined use of different classes of drugs enables treatment to focus on more than one viral target simultaneously.

Other therapeutics are also under investigation. These include an agent that targets integrase, and interferon, an immunomodulator. The latter is approved for treatment of Kaposi's Sarcoma and is being studied for its effects in combination with nucleoside analogs.

Lessons Learned

Dr. Feigal summarized the lessons learned to date from clinical trials regarding HIV therapies:

- Physicians should carefully consider the choice of initial therapy, because HIV drugs are most effective in therapy-naive patients.
- Monotherapy should not be the initial treatment approach; instead, physicians should start with the best drug combination available. The more severe the patient's disease, the more drugs should be used in combination.
- Patient compliance and adequate dosing are important. For example, patients who miss doses or who are on too low a dose develop resistance.
- Patients with low CD4 counts are producing a large number of CD4 cells; when viral replication is controlled, CD4 counts can rise dramatically.
- Viral load is a strong predictor of disease activity. (During the last year a kit for measuring viral load has been made commercially available to clinical labs.)
- Suppression of viral replication prolongs the usefulness of initially less effective drugs.

Participation in Clinical Trials

During his presentation, Dr. Feigal discussed the importance of minority group participation in clinical trials. Participation is integral to the development of new therapies, and it also increases a patient's treatment options. In addition, having sufficient numbers of minority study subjects helps provide an accurate assessment of a drug's treatment effects. For example, a Veterans Administration (VA) study of

early versus delayed AZT treatment showed that early treatment did not appear to have much benefit for Hispanics and African Americans. In this case, FDA examined pooled data from other studies and determined that the VA finding was a "false signal" because it was based on a relatively small sample of minority patients. Dr. Feigal also observed that another difficulty in detecting treatment effects is when the different effects are due to factors such as unequal access to health care.

Diabetes

The next panelist, **Dr. Wayman Cheatham** (Howard University College of Medicine) described new approaches for treating diabetes. He began by noting that diabetes is the third leading cause of death in the United States, affecting 16 million people. Of these, only 8 million have been diagnosed and less than one-half of these individuals are receiving appropriate treatment. In 1995, the cost of caring for and treating diabetic patients reached \$100,000 billion.

Risk Factors for Diabetes

Risk factors for diabetes include having a family history of diabetes, being overweight, advancing age, and being from a minority ethnic group. Dr. Cheatham explained that people of color are disproportionately affected by diabetes. One in 22 white Americans have the disease, compared with 1 in 14 African Americans, 1 in 7 Hispanics, and 1 in 3 Native Americans. He recounted that among the Pima Indian tribe of Arizona, 1 in 2 people over age 35 has Type II diabetes. Diabetes-related mortality rates are also higher among people of color than among whites.

Etiology of Diabetes

Diabetes is a condition characterized by elevated blood sugar. Affected individuals cannot use all of the glucose provided by the food they eat or produced by the liver. Dr. Cheatham emphasized, however, that diabetes is not **caused** by high blood sugar. High blood sugar is only a sign of the metabolic abnormalities that are collectively called diabetes. These metabolic abnormalities start long before blood sugar levels rise; therefore, early diagnosis and treatment can reduce or prevent diabetes-related morbidity and mortality.

Dr. Cheatham then offered the following classification system for diabetes mellitus:

- Type I (This usually occurs in children, but there are also many 60- to 80-year-olds with Type I. Individuals with Type I diabetes have an insulin deficiency.)
- Type II (This usually occurs in an older age group and is characterized by a gradual onset of symptoms.)
- Pregnancy complications

- Impaired glucose tolerance (Prevalence increases as people age and increase in weight.)

Dr. Cheatham described the process by which insulin binds to the cell receptor and transports glucose, sodium, potassium, and calcium to the cell, and noted that a number of different disorders can lead to glucose elevation. He noted that there are three disorders that represent Type I diabetes and five disorders that represent Type II diabetes. Interestingly, among the various ethnic groups, different genetic markers have been found that appear to cause the same type of disease.

Complications from diabetes include cardiovascular disease; eye, kidney, and nerve damage, and impotence. Dr. Cheatham noted that hypertension occurs in about 60 to 80 percent of people with Type II diabetes. Furthermore, there is thought to be a link between the resistance to insulin that characterizes people with Type II diabetes and changes in the way the cell responds to sodium and calcium. He commented that two studies are underway to evaluate patients with concomitant diabetes and hypertension.

Diabetes Diagnosis and Treatment

Currently, there is no way to diagnose diabetes other than measuring glucose levels. Research is underway, however, to discover markers that can identify people who are at risk for developing diabetes. In Type II patients, for example, hypertension usually occurs about 5 to 6 years before the blood sugar starts to rise. Cholesterol levels also change: high-density lipoprotein (HDL) levels decrease; low-density lipoprotein (LDL) levels (the "bad" type of cholesterol), increase. One diabetes prevention trial described by Dr. Cheatham will follow 4,000 individuals who have a risk for developing diabetes over a 7-year period. Fifty percent of study participants will be people of color.

Dr. Cheatham also presented an overview of the evolution of treatments (oral pharmaceuticals and insulins) to reduce glucose levels. In the 1940s, sulfonyl compounds, when taken orally, lowered glucose levels. Commercially available sulfonylureas became available in the 1950s, oral biguanides were discovered in the 1960s. By the 1970s, experiments were underway to premix fast and slow acting insulins to achieve the benefits of both in one preparation. In the 1980s insulin with the same amino acid structure as human insulin was introduced, followed by a second generation of sulfonylureas. In the 1990s, a third generation of sulfonylureas has been introduced, along with a new biguanide, and an alpha-glucosidase inhibitor. Other oral agents are "just around the corner," pending final evaluations.

Prostate Cancer

Dr. Judd Moul (Uniformed Services University of Health Sciences) explained that prostate cancer is now the most common cancer in American men. Between 1995 and 1996 new cases have increased by 30 percent. In 1996, more than 317,000 cases will be diagnosed; more than 41,000 men will die from the disease. Because many African-American men are unaware of their high risk for prostate cancer and lack access to cancer screening tests, they remain undiagnosed for a longer time than white men and consequently have more advanced prostate cancer at the time of diagnosis. As a result, the chance for

long-term survival is lower for African-American men than for white men.

Screening/Treatment Strategies

Dr. Moul reviewed recent advances in prostate cancer treatment of benefit to African-American men. Preventive measures include the development of the prostate specific antigen (PSA) blood test and new screening guidelines for African-American men. These guidelines resulted from a study of 5,000 men in U.S. Armed Forces. In this study, the PSA performed differently for African American men than for white men. African Americans with prostate cancer were about 2 years younger than white men, but had 1.3 to 2.5 times the tumor volume. Dr. Moul reported that the new guidelines recommend that (1) African-American men be screened beginning at age 40 and (2) the PSA "normal" range for African-American men be lowered to "2." Dr. Moul noted, however, that there is still no clear evidence that these preventive measures will be effective. More clinical trials are needed. Without this data, it is unlikely that managed care organizations will pay for PSA screenings.

Dr. Moul also reviewed other tests and therapies in development for prostate cancer:

- Free-PSA, RT-PCR for occult metastasis. Most PSA in bloodstream is bound to other proteins (bound PSA), but about 10 to 20 percent is "free." The lower the percentage of free PSA, the higher the probability for prostate cancer. However, the free-PSA test has not yet been approved by FDA.
- Surgical treatment (nerve-sparing radical prostatectomy). More African Americans are receiving this treatment, but the outcome is not as good as for white men. Treatment needs to occur earlier, when the cancer is smaller.
- Radiation treatment. In one type of radiation therapy, computers are used to localize the radiation beam; in another type of treatment, irradiated seeds are implanted in the prostate.
- Cryotherapy. Liquid nitrogen is pumped into the prostate to freeze the tumor. (Clinical trials are needed to determine long-term results.)
- "Watchful waiting" after a PSA test. Most of the current data is from white patients. For patients with low [Gleason] grade cancer, the outcome is good, but only 10-15 percent of patients have low grade prostate cancer at diagnosis. A new study, "PIVOT" is being conducted primarily in Veterans Administration sites, which is randomizing men to radical prostatectomy versus watchful waiting. The study is currently undergoing patient accrual.
- Watchful waiting is also the strategy to be used for benign prostatic hyperplasia (BPH). BPH is the noncancerous enlargement of the prostate and occurs in about 80 percent of men over age 50. BPH and prostate cancer are not necessarily linked, but men with BPH should be screened with PSA and a digital rectal exam.

- **Hormonal therapy.** This is used for a few months prior to surgery, radiation, or cryotherapy, to treat patients with metastatic prostate cancer. The goals are to decrease tumor size and increase long-term survival. Most patients respond for a while, but when they fail hormonal therapy, their options are limited. Clinical trials are urgently needed to develop new treatments for this type of prostate cancer.

Dr. Moul reported that the optimum treatment for prostate cancer is still unknown. Men of color are needed for clinical trials of diagnostic tools, new local treatments, and new hormonal and chemotherapy agents. To this end, more efforts must be made to increase awareness about prostate cancer among African-American men and encourage screening. Barriers to early detection--distrust, fear of cancer, reluctance to undergo a digital rectal exam --must also be overcome.

Finally, Dr. Moul observed that prostate cancer research is at least a decade behind that for breast cancer. More research funds are needed. He noted that the United States has "spent less on prostate cancer research than on a single jet fighter."

Panel: Diverse Perspectives of Clinical Trials

Moderator: Linda Ann Sherman, M.D.

Panelists:

FDA--Jonca [Bull](#), M.D., F.A.A.O.

Human Subject Protection--Warren [Ashe](#), Ph.D.

Patient--Gregory [Hutchings](#)

Community--Otis [Brawley](#), M.D.

Academia--Wayne [Greaves](#), M.D., F.A.C.P.

Industry--James [Powell](#), M.D.

FDA Perspective

Dr. Jonca Bull (FDA) presented an overview of FDA's drug approval process. First, she noted that the agency's mission is to enforce Federal law and FDA regulations to protect the consumer's "health, safety, and pocketbook." She then offered an historical perspective of drug regulation in the United States and reviewed FDA's growing consumer protection responsibilities. Milestones included the passage of the Food, Drug, and Cosmetic Act, and the emergence of human subjects protection as a paramount agency concern.

She stated that the regulatory function of FDA's Center for Drug Evaluation and Research (CDER) is to approve drugs for marketing that (1) are effective for their labeled indications, (2) provide benefits that outweigh their risks, and (3) have labeling for use that is complete and honestly communicated. She distinguished between drugs, biological products (e.g., vaccines, blood products), and medical devices.

Each is handled somewhat differently in the development and approval process.

Dr. Bull then described the process of moving a drug from discovery to the marketplace. After a drug is shown to have promise in terms of efficacy and an adequate measure of safety for humans, it moves into clinical trials to test for effects in humans. Clinical trials are categorized into the following phases:

- Phase I -- Small studies, usually involving 20 to 100 patients, for the purpose of determining safety.
- Phase I -- Larger studies, involving up to several hundred subjects, to further explore safety and to determine effective dosage for a specific indication.
- Phase III -- Still larger studies, involving up to several thousand subjects, for the purpose of assessing safety, efficacy, and dosage and to better characterize the drug for its intended use.
- Phase IV -- Post-approval studies to further characterize the drug. For HIV drugs, which are approved on the basis of surrogate markers (e.g., CD4 counts, changes in viral load), these studies are intended to document the drug's clinical benefit. If the drug shows no clinical benefit, the sponsor is required to voluntarily withdraw the drug from the market. Phase IV trials also enable sponsors to evaluate the drug in populations that may not have been well represented in the Phase III trials.

Next, Dr. Bull explained FDA mechanisms for evaluating promising new drugs: Investigational New Drug applications (INDs), New Drug Applications (NDAs), and Abbreviated New Drug Application (ANDAs). An investigational drug is a drug that has not been approved for use in human subjects. The drug sponsor is required to submit an IND application, which contains an exemption permitting the drug to be studied in humans. The FDA has a 30-day time limit to review the application and either grant or withhold an exemption.

After the IND is allowed to proceed, the sponsor moves the drug into clinical research trials (Phases I, II, and III). This process culminates in the preparation of an NDA, for the purpose of marketing the new drug. Dr. Bull explained that the NDA usually involves thousands of pages, and includes chemistry, pharmacology, toxicology, and other sections. The NDA is intended to provide clinical guidance for the optimum use of the drug for a specified indication. The package insert that accompanies the marketed drug includes a description of the product information on dosage and administration, contra-indications, adverse reactions, etc.

When evaluating a drug, FDA seeks to determine that the drug has been tested in patients who are similar in demographics to the group who will be using the drug. FDA also ensures that efficacy and safety have been assessed. In addition, FDA assesses:

- Drug-demographic interactions to identify demographic features that could alter the metabolism

or distribution of the drug or be associated with altered efficacy or adverse events; and

- Drug-disease interactions to identify disease features that could alter the metabolism or distribution of the drug, or be associated with more frequent or more severe adverse events.

Dr. Bull noted that FDA's regulatory function does not stop with drug approval. She described FDA's MedWatch Program, which enables side effects to be reported after the drug has entered the market. (The MedWatch program is accessed through a toll-free number and reports are handled with strict confidentiality.) If problems arise, FDA can issue "Dear Health Professional" letters to alert physicians, change product labeling or packaging, or institute a product recall or withdrawal.

Human Subjects Protection

Dr. Warren Ashe (Howard University College of Medicine) spoke about the issue of protecting subjects who participate in clinical trials. The primary mechanism for this is the Institutional Review Board (IRB), which is established by the institution conducting the study and is responsible for reviewing all protocols that involve human subjects. IRBs are composed of community representatives, nonscientists, and ethicists.

During his discussion of the origins and history of IRBs, Dr. Ashe noted that outrage over the Tuskegee Syphilis study marked the beginning of this country's sensitivity to human subjects protection. Dr. Ashe reviewed the regulations that led to the establishment and refinement of the IRB process, noting that the "challenge is to make sure that every individual is protected." This means establishing procedures so that "informed consent is indeed informed consent and not an inducement or a coercion to participate in a research program."

Dr. Ashe acknowledged, however, that concerns remain among subjects who are recruited to participate in clinical trials. Therefore, the success of recruiting women and minorities in clinical trials depends on several factors. These are outlined below.

- Recruitment procedures must be carefully considered. Dr. Ashe suggested that recruiters "come from the community." He cautioned against having recruiters "show up in a white coat" because it can be extremely intimidating for prospective study subjects.
- Methods for obtaining informed consent must clearly explain the purpose of a clinical trial to prospective study subjects. Subjects must be assured that they can withdraw at any time from the trial without any penalty.
- Study subjects should be told about risks and benefits of participation. Possible side effects should be described in lay terminology.
- Study subjects must be confident that any new, beneficial information about treatment developed

during the trial will be available, even if it means that they stop participating in the trial.

- Study investigators should "use language that people can understand" and make it appropriate to an eighth grade reading level.
- Compensation for participation must be commensurate with the risk; otherwise, the compensation could be construed as an inducement that would compromise true informed consent.
- The IRB needs to monitor the trial to ensure that protocol is being followed.

Other considerations for the development of informed consent protocols include the following:

- Informed consent should include a comprehensive discussion about what is currently known about the drug and any possible long-term limitations. For example, taking the study drug might preclude taking other therapies at a later time. In the case of protease inhibitors, the patient should be aware of the enormous expense of continuing the drug once the study ends.
- The study description should be written in lay language and can be as extensive as the investigator wishes. It could include background information describing why the study is being conducted, and a section describing what the expected outcomes are. One drawback, however, is that the consent form can become too lengthy. The impetus for informed consent would still require that the investigator and patient "plow through it." If necessary, the investigator should review the form repeatedly until the patient fully understands its content and implications.

Patient Perspective

Mr. Gregory Hutchings (D.C. Agency for HIV/AIDS) offered his perspective, as an HIV-positive African American who had participated in several HIV drug treatment trials. He suggested that people wanting to participate in clinical trials "find out exactly what is happening" in the clinical trial, in terms of type of medication, dosage regimen, side effects, etc. He suggested talking to other people who have taken the drug and reading any available literature about the drug.

He commented that he, like many African Americans, is very cautious when it comes to participating in clinical trials for experimental drugs; consequently, he prefers to enroll in trials of already approved drugs. Mr. Hutchings observed that many patients are unaware of the many trials being conducted with nonexperimental drugs. He recommended that investigators offer patients an opportunity to enroll in these studies of nonexperimental agents, noting that "it's a good **in** for getting people involved [in their first clinical trial] and gaining their trust."

Other strategies suggested for building trust with prospective study subjects and facilitating trial enrollment are noted below:

- Have "culturally competent" staff administer the trials.
- Make patients feel as comfortable as possible and convey that "you're not this person of authority who is...enticing them into doing something that they don't want to do." Make it clear to patients that they can choose not to participate.
- Ensure that written materials are "reader accessible."
- Let patients know that there are other patients, from the same ethnic background, who are participating in the trial.
- Use nontraditional methods to recruit patients. Design the trial enrollment announcement so that it "gears that person to wanting the information, to want to get involved . . ." In addition to posting notices on bulletin boards or in the newspaper, "get out and talk about it."
- Suggest that the patient's private physician also monitor for drug effects.

Mr. Hutchings observed that even the **perception** of unethical behavior on the part of clinical trial organizers can damage chances for recruiting people of color. He added that the "only way we can involve community members in participating in clinical trials is to be able to explain how [Tuskegee syphilis study] can't happen again."

Community Perspective

Dr. Otis Brawley, National Cancer Institute (NCI), spoke about clinical trials programs sponsored by NCI. First he noted that only about 3 percent of cancer patients participate in clinical trials. To increase patient access to trials, NCI sponsors ten cooperative groups involving nearly 500 academic and community hospitals that run cancer-related clinical trials. These groups accrue nearly 30,000 patients annually to cancer treatment trials and nearly 20,000 healthy people to cancer control studies (i.e., primarily screening and prevention studies).

Minority-Based Community Clinical Oncology Program

In 1990, NCI established its Minority-Based Community Clinical Oncology Program (MB-CCOP). The program funds groups of physicians and hospitals that care for large numbers of minority patients for the purpose of enrolling minority patients into NCI clinical trials. Between 1991 and 1994, about 14 percent of patients in NCI cooperative group and cancer center trials self-identified as a minority. Ten MB-CCOPs accrued about 10 percent of all minority patients entering NCI-sponsored treatment trials during this period. The MB-CCOPs maintains a log of all newly diagnosed cancer patients seen by the centers. (This log is expected to provide important insights into the dynamics of minority patient accrual.)

NCI-Sponsored Cancer Treatment Trials

Dr. Brawley described studies to determine the extent to which African Americans and Hispanics participate in NCI-sponsored treatment trials. The first study analyzed demographic data from 7,809 newly diagnosed adult patients seen at 12 MB-CCOP sites. Enrollment rates for whites, Hispanics, and African Americans were similar. Of 820 patients eligible to enroll in a trial, 62 percent of the whites, 70 percent of the Hispanics, and 61 percent of the African-American patients enrolled. Dr. Brawley believed this demonstrates that hospitals that have a good relationship with their communities can enroll Hispanics and African Americans at rates similar to whites.

Another study described by Dr. Brawley examined data from nearly 100,000 patients accrued to NCI-sponsored cooperative group trials between 1992 and 1994. These data also showed African-American, white, and Hispanic patients to be proportionally represented. Indeed, in some cases African Americans and Hispanics are overrepresented. For example, 10.3 percent of men with prostate cancer are African-American, but 14.7 percent of men in NCI prostate cancer studies are African American. Similarly, 4.8 percent of leukemia patients are Hispanic, but 9.5 percent of patients in NCI leukemia trials are Hispanic.

NCI-Sponsored Cancer Prevention Studies

Dr. Brawley observed that although NCI cooperative group accrues large numbers of minority patients to treatment trials, it is unable to achieve similar success for prevention and control trials. For example, in NCI's Prostate Cancer Prevention Trial (which is being managed by an African-American physician) only 4 percent of the 18,000 subjects are African American and only three percent are Hispanic.

Dr. Brawley suggested that the reasons for the disparity in ethnic enrollment patterns could be related to the following. Prevention studies (i.e., studies of healthy people) attract the individuals who are highly educated and economically secure. In the prostate prevention trial, for example, 37 percent of all 18,000 enrollees had a post-baccalaureate degree, compared with 31 percent of 900 African-American enrollees. Dr. Brawley observed that the people who participate in prevention studies "can afford to take time off from work twice a year to go to the doctor for a problem they do not have."

Dr. Brawley noted that some people have called for proportional representation in clinical trials, assuming that proportional representation allows for an analysis to determine if one intervention is more effective in one population than another. He cautioned that proportional representation rarely provides statistical power needed to reach any firm conclusions. He added that, fortunately, clinically relevant differences among different ethnic populations are likely to be rare. It was also noted that the ease or difficulty in recruiting depends a great deal on the expectations for the product being studied in the trial.

Academia's Perspective

Dr. Wayne Greaves (Howard University College of Medicine) shared his perspective as a clinical investigator for an academic center. Dr. Greaves began by observing that academic centers continue to

play an important part in the conduct of clinical trials, and they offer unique opportunities for teaching and patient care. He also noted that patients who participate in clinical trials have several advantages; specifically, free care, flexible appointment schedules, access to new treatments, and access to experts in the field.

Challenges Faced by Investigators at Academic Institutions

Dr. Greaves noted, however, that investigators in academia face many challenges. First, they must meet exacting scientific and regulatory standards. Careful recordkeeping is a key part of this challenge. Second, they must recruit research subjects from a population that is increasingly skeptical of research. Third, investigators at academic centers face intense competition from (1) organizations that can offer incentives (e.g., free care) previously available only in the academic setting and (2) for-profit research organizations that are often able to outperform academic centers in conducting clinical trials. All this results in greater competition for the research dollar.

A related issue is that minority institutions find it difficult to compete with "Ivy League" institutions for research grants from the pharmaceutical industry. Dr. Greaves observed that if drug companies believe they can get their products to market "faster through Johns Hopkins or Yale, then that's what they'll do." During the discussion period, it was also noted that pharmaceutical companies often "try to take advantage of the naivete" of minority institutions like Howard by offering them less funds than they would offer Ivy League institutions to conduct similar research.

In addition to these challenges, the academic researcher also has heavy clinical and teaching obligations that have to be coordinated with the research activity. Another pressure for academic investigators is the need to "publish or perish." "Town vs. gown" tension represents another challenge to overcome. To facilitate clinical trial referrals, it is essential that academic investigators build good relationships with physicians in the community.

Other challenges include the following:

- Protocol approval by the IRB is often protracted.
- Remuneration is made directly to institution.
- The study outcome is unknown for years.

Barriers to the Participation of Minority Academic Institutions

Dr. Greaves also commented on several barriers that prevent minority academic institutions from participating in clinical research. Traditionally, the emphasis is on teaching and the provision of care; research is less of a priority. Another barrier is that becoming a research center requires enormous financial resources, which minority institutions seldom have. Yet another barrier is that physicians at

minority institutions may not be as interested in referring patients to trials for an experimental therapy as they are in providing their patients with good care. Therefore, it is not surprising that researchers at Howard University, for example, have had "a fairly difficult time recruiting patients for our clinical trials, even though we are a minority institution, and even though we are minority investigators."

Qualities of a Successful Clinical Investigator

Dr. Greaves offered the following observations about the qualities of a successful clinical investigator. The successful investigator is one who is knowledgeable about clinical trials, motivated, plans ahead, develops a trained research team, hires skilled administrative staff, clarifies the role and obligations of the study sponsor, and involves patients in study implementation. Knowledge of administrative and budgetary aspects of clinical trials are also critical to ensure smooth study implementation.

Successful clinical investigators also need to handle the following logistical issues:

- Recruiting qualified personnel; training and supervising staff; and conducting periodic reviews of staff
- Establishing and managing the budget
- Working closely with the IRB
- Recruiting study subjects and communicating with referring physicians
- Holding regular meetings with the study team

Also key to an investigator's success is avoiding the potential pitfalls that characterize clinical trial management. Pitfalls include:

- Not clearly explaining informed consent
- Signing documents before reading them
- Hiring unqualified personnel
- Not reading protocol carefully
- Not reporting adverse events promptly
- Conducting too many studies at once

- Over delegating work/not supervising closely
- Improperly administering the budget

Recruitment Challenges for HIV Trials

During his presentation, Dr. Greaves also discussed the difficulty recruiting people of color for HIV clinical trials. HIV is characterized by many sensitive ethnic and lifestyle issues. For example, some patients find it difficult to acknowledge their seropositive status. In addition, there are few HIV activists in communities of color, as compared with white gay communities. In addition, HIV patients are frequently on many medications, and adverse drug interactions are common. Moreover the "gold standard keeps shifting," for example, from AZT monotherapy to combination therapy. This makes it hard to recruit and retain patients in long-term trials.

Industry Perspective

Dr. James Powell (Proctor and Gamble) discussed how the pharmaceutical industry selects investigators for its clinical trials. First, Dr. Powell noted that the involvement of primary care physicians is key to maximizing the quality of care available to patients and urged symposium attendees to participate in the drug development process as clinical trial investigators. Dr. Powell reviewed sponsor's expectations of the clinical investigator, discussed the potential benefits and rewards, and examined strategies to expand opportunities for those interested in becoming an investigator for industry-sponsored trials.

He stated that the discovery, development, manufacture, and marketing of new pharmaceutical products is a complex, multidisciplinary process. The complexity derives from the array of laboratory and manufacturing controls required and the need for data from human and other sources to support the product's proper, safe, and effective use.

From the industry's perspective, the factors that drive drug development are regulations, time, and cost. Regulatory drivers include good clinical practices (GCP) guidelines that ensure a basic level of quality in the conduct of the trials and the data obtained. Other regulations require that drug sponsors prove the safety and effectiveness of their products and that they have enrolled subjects that reflect the target population. To meet these requirements, drug sponsors design protocols to collect the necessary data, often with input from the regulatory authorities.

Data generated by the clinical trial are property of the drug sponsor. Often sponsors also seek to have the final rights on any publications that might result from the trial.

Other factors that drive drug development are cost and time. It costs about \$500 million to bring a new drug to the marketplace (through Phase III trials). The time from drug discovery/concept to the marketplace is at least 10 years. Excluding patent extensions, the drug sponsor has about 7 years to

recoup its investment in the marketplace. The revenue loss that occurs when a patent expires and the beginning of competition from generic brands "makes timing a matter of survival for the industry." In fact, noted Dr. Powell, "time is not just money; time is more important than money."

Dr. Powell elaborated on the regulatory requirement that the investigator be qualified in terms of training and experience. The "ideal" investigator:

- Meets requirements for training and experience
- Has the time, resources, and staff to conduct the study
- Complies with regulatory requirements and adheres to the study protocol
- Knows the target patient population and demonstrates the ability to recruit subjects
- Understands the sponsor's priorities and intent
- Delivers the data on schedule and communicates issues in a timely manner
- Has experience with the type of study being undertaken

Dr. Powell reviewed the benefits to investigators who undertake a clinical trial: access to new therapies, considerable financial return, site development support (e.g., new equipment, staff), and publication opportunities.

Dr. Powell discussed a strategy used by drug sponsors in need of "instant" organizational capacity. Instead of contracting with a single investigator, the drug company links with a contract research organization (CRO). In the CRO arrangement, the sponsor carries the staffing cost only for the time needed to conduct the trial. CROs are selected for their experience with the type of study, access to qualified investigators, focus on "getting the job done," and awareness of regulatory issues.

Dr. Powell suggested that symposium participants who wished to establish themselves as clinical trial investigators demonstrate "interest, capability, and access." For example, become a "sub-investigator" for a study being conducted by a local hospital or academic center. This provides an opportunity to (1) become familiar with the extensive documentation required for clinical trials and (2) gain a working knowledge of GCP requirements. Dr. Powell also suggested that prospective investigators contact the drug sponsor or CRO directly.

Dr. Powell stated that FDA and PHARMA have held some discussions about improving minority/investigator recruitment. He noted that the pharmaceutical industry is required to include representation of the target population in its studies. He observed that industry collaborations with the "usual" academic sites may not allow investigators to obtain broader access to minority study subjects. It was also noted

by Dr. Bull that representation should be relevant in terms of disease prevalence among the target population, in addition to demographically relevant.

Panel: Expanded Access Mechanisms and Managing Costs of Clinical Trials and Investigational Therapies

Moderator: Theresa Toigo, R.Ph., M.B.A.

Panelists:

Expanded Access--Heidi [Jolson](#), M.D., M.P.H.

AIDS Drug Assistance--Steven [Young](#), M.P.H.

Managed Care--Mary [McCabe](#), R.N.

Medicaid/Medicare--Gerald [Zelinger](#), M.D.

Expanded Access

Dr. Heidi Jolson (FDA) focused on the concept of "expanded access" and the regulatory mechanisms developed by FDA to expedite the availability, development, evaluation, and marketing of new therapies. Dr. Jolson explained that these mechanisms are intended to make investigational therapies available to people with serious or life-threatening illnesses and without other treatment options, before the therapies receive approval from FDA. In addition to enhancing access to promising new therapies, the expanded access mechanisms provide important information on a drug's safety and efficacy -- without compromising the patient's safety and the integrity of the clinical trial evaluation.

Dr. Jolson pointed out that the expanded access procedures reflect FDA's recognition that physicians and patients are generally willing to accept greater risk or side effects to treat life-threatening illnesses.

Although the primary objective is patient treatment, FDA encourages drug sponsors to design the programs in such a way as to obtain meaningful data that can be collected to further knowledge about the drug. All of the expanded access programs share common features: They are "open label;" that is, physicians and patients alike know what drug the patient is receiving. In most cases patients in the program only have one choice of drug, although occasionally different groups of patients take different doses of the drug, allowing for dose comparisons. Drugs used in the program must have demonstrated a degree of efficacy, either *in vitro* or in clinical studies.

Dr. Jolson explained the five mechanisms for expanded access. These are summarized below.

Group C Drugs

This is a mechanism specifically for the development of cancer therapies and represents a collaboration between the National Cancer Institute and FDA.

Emergency Investigational New Drug (E-IND)

In this mechanism a physician calls FDA and/or the pharmaceutical company directly and requests that the investigational drug be made available to a specific patient. The drug manufacturer must also be contacted to initiate shipment of the drug. In this type of emergency situation, a written submission is unnecessary; however, FDA expects the physician to submit an IND application as soon as possible. In 1995, 624 E-INDs were issued by FDA's Division of Antiviral Drug Products.

Open Label Protocol

This is the most commonly used expanded access mechanism and used if a physician or pharmaceutical company expects to request a drug for multiple patients. FDA prefers that the sponsor develop a treatment protocol, instead of contacting FDA on a patient-by-patient basis. The open label for 3TC, a promising AIDS drug, enrolled over 32,000 patients and involved about 1,400 investigators before the drug was approved for marketing. One drawback to this mechanism is that drug sponsors seldom manufacture large quantities of a drug prior to its final approval by FDA.

Treatment IND (T-IND)

This mechanism is similar to the open label protocol, except that the T-IND occurs later in drug development. It is meant to bridge the time between when controlled clinical trials are almost complete and the new drug application is approved. The T-IND protocol needs to include: intended use, patient eligibility criteria, route and dose information, safety monitoring reports, and the investigator's brochure. Compliance with the patient safeguard processes must also be demonstrated (e.g., informed consent). Between June 1987 and September 1996, 38 Treatment INDs were granted: 13 cancer drugs, 11 HIV drugs and the remaining 14 for a variety of other serious and life-threatening diseases. All of these drugs were eventually approved by the FDA.

Parallel Track

This mechanism was established in 1992 specifically for HIV therapies and provides patients with access to new therapies very early in the drug development process. Under this mechanism, expanded access is provided in parallel (i.e., concurrently) with clinical trial investigations. The mechanism is fairly cumbersome, in that it requires coordination between the National Institutes of Health and FDA. Thus far, it has only been used once, for d4T (Stavudine). The mechanism provides explicit criteria to protect patients and the clinical trials process.

To demonstrate the effectiveness of the expanded access programs, Dr. Jolson presented a chart with information about HIV therapeutics. To date, more than 80,000 HIV-positive patients have received antiretroviral therapies prior to FDA approval. The data indicated that the enrollment of women has improved slightly since 1986 and that minority enrollment has been consistently about 20 percent.

AIDS Drug Assistance

Steven Young, Health Resources and Services Administration, discussed provisions of the Ryan White Comprehensive AIDS Resources Emergency (CARE) Act that provide ways to expand patient access to investigational therapies. The Care Act offers nearly \$1 billion in funding to help communities respond

to the needs of people with HIV. Title I of the CARE Act provides funds to cities and metropolitan areas especially hard hit by the HIV epidemic. The Title I funding formula is based on the number of residents who are living with HIV and its purpose is to provide financial relief for services that have no other source of payment. Supplemental funds can be granted, depending on the needs of special populations (e.g., people of color, homeless, substance abusers, etc.) within that metropolitan area. Currently, 49 Emergency Metropolitan Areas (EMAs) receive funds. Funds are used for a broad range of outpatient health care services (e.g., medical, dental, substance abuse).

Title II of the CARE Act provides funds directly to the states to improve the quality and availability of primary care services. Under Title II, the states determine how the funds are to be channeled: through HIV care consortia, home and community-based care, health insurance reimbursement, or AIDS drug reimbursement.

AIDS Drug Assistance Program

Mr. Young explained that the CARE Act provides approximately \$220 million for the AIDS Drug Assistance Program (ADAP). In 1995 the ADAP program served nearly 70,000 patients: 41 percent were white, 29 percent were African American, and 28 percent were Hispanic. ADAP provides reimbursement for FDA-approved drugs that treat HIV or prevent the serious deterioration of health caused by HIV. The program also reimburses for ancillary devices (e.g., tubing, nebulizers). The formularies for reimbursement are established by each state and, therefore, can vary widely. Mr. Young cautioned that many states are placing reimbursement caps on their programs, because they lack the financial resources to pay for the new, highly effective -- and expensive -- AIDS drugs (i.e., protease inhibitors).

Outreach to Improve Patient Access to Investigational HIV Drugs

Title I and Title II funds may **not** be used to support the costs of conducting clinical trials, including administrative costs and patient monitoring. However, the funds can be used to conduct patient outreach to promote enrollment in clinical trials and expanded access programs. The funds can also be used to reimburse for complementary (i.e., alternative) therapies. Mr. Young cautioned against using the term "alternative" because it elicits "a very bad reaction from politicians and budget folks" who see it as a "way around the system." He noted that most people, however, understand the need to complement the traditional medical approach.

Mr. Young also described other CARE Act provisions to expand patients' access to investigational therapies. The CARE Act provides funding support for:

- Clinical trials volunteer networks. For example, the D.C. HIV Care Consortium provides "dual" referrals, linking community providers with clinical trial investigators and vice versa.
- Targeted outreach. Several cities and states operate computer databases that list all the clinical

trials in the area and patients that want to volunteer for clinical trials.

- Public information campaigns (brochures, radio advertisements, posters, etc.).
- Case managers are supported in their efforts to develop formal relationships with local clinical trial programs and facilitate patient referrals to these trials.
- Primary care physicians are supported for participation in expanded access or compassionate use programs.

Finally, Mr. Young discussed Title IV, which focuses on women, children, and families with HIV. Grants are now being offered under this Title to increase the participation of women and children in clinical trials. Another provision in Title IV relates to improved coordination between the National Institutes of Health and HRSA.

Managed Care

Mary McCabe (National Cancer Institute) reviewed the impact of the "managed care" service delivery and reimbursement system on the conduct of clinical cancer research. She stated that financial support for this research previously had been shared by the Federal Government, pharmaceutical industry, private institutions, and third party payers.

There is now, however, widespread uncertainty about future support for clinical research, chiefly because the managed care system is driven by economic incentives and will not support the costs of caring for patients who are receiving experimental therapies. As managed care systems proliferate, cancer patients and health professionals are also voicing concerns about the future quality of cancer treatment and continued access to promising therapies through clinical trials. This has particularly important implications for communities of color because minority access to clinical trials is closely linked with the provision of quality health care.

The changes in clinical trial coverage brought about by managed care are noted below:

- Reduced financial incentives. These result in fewer referral opportunities for patients, limited reimbursement to participating physicians, and less interest in developing answers to research questions.
- Constraints on physicians practices. Investigators lack the time and resources to participate in clinical trials. For example, how does a physician ensure a patient's informed consent when the time to explain the trial is limited.
- Constraints on institutions. Traditional referral networks are disrupted, making it harder to for physicians to refer patients to the academic center or hospital that is conducting a specific trial.

- Limited access for patients. Underinsured/uninsured patients have fewer opportunities to access trials. Patients have limited out-of-plan referral options, uneven benefits, and inconsistent coverage.

Ms. McCabe reviewed current NCI initiatives to address the issues raised by managed care. These include agreements between NCI and managed care organizations. The Department of Defense, for example, has agreed to cover participation of CHAMPUS members in NCI-sponsored treatment trials. The Veterans Administration has entered into an even broader agreement that will cover participation in NCI prevention trials. The Blue Cross/Blue Shield's Pediatric Cancer Network has agreed to ensure clinical trial access for children covered under these plans.

Other NCI initiatives includes linkages with the HMO Research Network, which serves a large minority population, regional Cancer Center networks, and the development of Federal and State legislation to provide coverage for cancer-related clinical trials.

Ms. McCabe concluded by offering the following recommendations for ensuring expanding patient access to clinical trials:

- Increase public awareness regarding the importance of clinical research and patient access to clinical trial participation.
- Encourage physicians to enroll patients in trials, despite the financial disincentives.
- Conduct more efficient, more economical clinical trials that conform as much as possible to the standard of care.
- Incorporate more endpoints of interest -- to patients and third-party payers-- into clinical trial protocols (e.g., cost-effectiveness and other economic endpoints; quality of life and functional improvement endpoints).

Medicaid/Medicare

Dr. Gerald Zelinger, Health Care Financing Administration (HCFA), stated that in recent years, Medicare and Medicaid, the two publicly financed health care programs administered by HCFA, have expanded their coverage of investigational and experimental therapies and procedures.

Medicare

Dr. Zelinger explained that Medicare covers people age 65 and older, those of any age who are disabled, and those of any age with end stage renal disease. The Social Security Act (Title 18) states that Medicare can cover only "reasonable and necessary" items and services. The traditional interpretation of this

statutory language is an assessment of whether a therapy is safe and effective, medically appropriate, not investigational or experimental, and not excluded from coverage by the Social Security Act.

Dr. Zelinger acknowledged that what is considered investigational or experimental often "resides in the beliefs of the person or agency you are talking to." Recently HCFA has been expanding its Medicare coverage of new medical technologies, transplant procedures, and drugs. For example, 90 percent of kidney transplants are covered. Medicare will cover FDA approved drugs for their labeled indications; off-label indications are left to the discretion of the Medicare contractor. HIV antiretrovirals (e.g., FDA-approved protease inhibitors) and self-administered drugs (e.g., oral prescription drugs) are not covered.

He noted that HCFA is in the process of developing a final rule regarding how coverage determinations will be made. This is expected to be published in late 1997. The final rule may include considerations for covering Treatment INDs.

Medicaid

The statutory basis for this program is Title 19 of the Social Security Act. The program pays for medical services for certain groups of low-income individuals (i.e., disabled, aged, blind, pregnant women, children, and single parents). Dr. Zelinger noted that neither the Medicaid statute or regulations discuss or define investigational therapies. Medical necessity is only briefly mentioned in regulation.

Medicaid is a joint Federal/State entitlement program, but each state has considerable discretion in implementing its own program. States have flexibility in determining what is considered investigational, experimental, or medically necessary. Even when a state determines that a procedure is investigational or experimental, the state may still decide to cover it. For example, HIV viral load tests were covered prior to their approval by FDA.

Under the Medicaid Drug Rebate Act of 1991, States are required to cover all FDA-approved drugs of manufacturers who have signed an agreement with FDA. Thus, Medicaid, unlike Medicare, covers FDA-approved antiretrovirals.

Medicaid and Managed Care

Approximately one-third of Medicaid beneficiaries are enrolled in managed care plans, compared with 12 percent of Medicare beneficiaries. Because Medicaid managed care plans are bound by their contracts with the States, they may not use formularies to determine drug coverage. Recently, HCFA has begun to inform its managed care plans that they must cover drugs that would be available to Medicaid patients in the fee-for-service setting. Thus, for example, Medicaid managed care plans must cover antiretrovirals like the protease inhibitors.

Dr. Zelinger echoed Ms. McCabe's assessment of the difficulty in getting managed care to participate in clinical trials, chiefly because the plans are unwilling to "lose control" of their patients and patient care

costs. He observed that it may be unfair for managed care plans to benefit from clinical trials without having to participate in some way. Nonparticipation also deprives managed care patients from receiving treatments early on.

Adjournment

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APPENDIX 1

Symposium Faculty

Warren K. Ashe, Ph.D.

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**Symposium Held on October 25, 1996
Howard University, Washington, DC**

END

KRA Corporation
1010 Wayne Avenue
Suite 850
Silver Spring, Maryland 20910
December 26, 1996

This document was prepared under Contract Number 277-95-2024 between the Howard University College of Medicine in cooperation with Maryland Aids Professional Education Center and KRA Corporation of Silver Spring, Maryland. The contents of this document do not necessarily reflect the views or policies of the Department, nor does mention of trade names, commercial products, or organizations imply endorsement by the U.S. Government.

HTML coded and placed on the web by:
Office of Special Health Issues
Food and Drug Administration
July 10, 1998

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