



Major Deficiencies in the Design and  
Funding of Clinical Trials:  
*A Report to the Nation Improving on How  
Human Studies Are Conducted*

**Findings of the  
Eliminating Disparities in Clinical Trials Project  
(EDICT)**

Chronic Disease Prevention and Control Research Center at  
Baylor College of Medicine

In collaboration with the Intercultural Cancer Council

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## PREFACE

Clinical trials are a critical resource for the discovery of new, life-saving drugs and for developing better prevention and diagnostic screening methods. Today's most effective prevention and treatment modalities are based on previous clinical trial results.

But while the need for clinical research is undisputed, how clinical trials are now conducted remains problematic. Increasing research finds major deficiencies in the way clinical trials are designed, carried out and funded in the U.S. with serious implications for the outcomes of medical research studies.

Of key significance for the future of scientific innovation is the exclusion or under-representation of women, older people, minorities, disabled persons, and rural populations in the vast majority of the research studies conducted in the U.S. Without adequate representation of all patient populations, researchers cannot learn about potential differences among groups and cannot ensure the generalization of results.

Contributing to the deficiencies in the design of clinical trials are numerous behavioral, social, economic, medical, and policy-related factors that must be addressed if the biomedical research community -- government researchers, academic centers and other non-profit sponsors, and industry scientists -- is to meet the complex healthcare needs of an ever more diverse U.S. population. This includes mistrust among many patients that they will receive the best treatment, the lack of awareness among clinicians about available clinical trials, lack of physician referral, and the strict inclusion and exclusion eligibility criteria that are commonly reported barriers to clinical trial participation. Moreover, how clinical trials are conducted in the U.S. is affected by federal policies and research protocols that perpetuate disparities by not requiring inclusion of all affected patient populations from the beginning.

Addressing the deficiencies in clinical research is more than an issue of fairness. These issues affect the very promise of clinical research: that when studies find a therapy or medical device works as intended in trial subjects, that result can be applied to the larger patient population. That is why addressing this persistent and pervasive problem cannot wait.

Today, extensive research data exist that point to actions that can be taken now to improve the clinical trials process. Accordingly, the Chronic Disease Prevention and Control Research Center (CDPCRC) at Baylor College of Medicine in Houston and the Intercultural Cancer Council (ICC) initiated the EDICT (Eliminating Disparities in Clinical Trials) Initiative, a multi-year process funded by Genentech, Inc. to review relevant policies of public, private and non-profit sponsors of clinical trials to identify problems and prescribe solutions.

Involving more than 300 public health officials, medical researchers, and patient advocates who worked in teams over several years, EDICT assessed the extent of disparities in clinical trials, the resulting health and economic costs, and the underlying factors. These EDICT teams also focused on two areas of chronic disease – cancer and asthma – to generate non-disease specific policy recommendations that can plausibly be applied to other disease profiles.

What follows is the result of this review, which focuses specifically on identifying those action steps that can positively impact the three R's of clinical trial participation: 1) recruitment, 2) retention, and 3) return (post-trial benefit) for underserved patients.

As such, this report serves as a blueprint for action by all stakeholders. To reduce the barriers to clinical trial participation requires an ongoing partnership through which policymakers, regulators, the public health community, clinicians, the pharmaceutical industry, and patient advocates can share resources and good ideas, while working toward a common goal. It is intended that this report will be a catalyst for this necessary and important collaborative effort.

## EXECUTIVE SUMMARY

At the same time that medical science has made possible new therapies for treating AIDS, cancer, and other once fatal diseases, there are major deficiencies in the way clinical trials are designed, carried out and funded in the U.S. with serious implications for the public health community.

Of critical concern is the fact that despite numerous years of discussion and the implementation of new federal and state policies, very few Americans actually take part in clinical trials, especially those at greatest risk for disease. Of the estimated 80,000 clinical trials that are conducted every year in the U.S., only 2.3 million Americans take part in these research studies – or less than one percent of the entire U.S. population.

Looking specifically at cancer clinical trials (where much has been published about the composition of clinical trials), only about 3 to 5 percent of the 10.1 million adults with cancer in the U.S. participate in cancer clinical trials. And the composition of these trials does not mirror those in the population with the highest rates of cancer. Although more than 60 percent of all cancers occur in older Americans, only 25 percent of those taking part in cancer studies in 2003 were over 65 years of age.<sup>1</sup> Older Americans are also routinely left out of clinical trials studying diseases associated with aging, such as Alzheimer's disease, arthritis, and incontinence.<sup>2</sup>

Compounding the problem, the vast majority of eligible adults -- women, racial and ethnic minorities, and those living in rural areas -- are also significantly under-represented in the make up of clinical trials. Among those who participated in clinical trials to test new cancer drugs between 1995-1999, less than 10 percent collectively represented African Americans, Asian/Pacific Islanders, Hispanics and Native Americans, according to an FDA review.<sup>3</sup> Further, a study published in *Cancer Causes and Control* found that as of 2006, no studies examined the impact of sexual orientation on recruitment of women to breast cancer clinical trials.<sup>4</sup>

Far more than just a fairness issue, the under-representation of specific populations in clinical trials is at direct odds with the current state of medical science and drug discovery. With the successful sequencing of the human genome, scientists are faced with the new challenge of documenting, describing and understanding the non-random pattern of human genetic variation and its link to disease risk in different patient groups. Findings from the large amount of genetic data generated to date show that more than 90 percent of the observed genetic variations occur within rather than between groups.<sup>5</sup> This underscores the fact the ethnicity -- which incorporates multiple variables including genetics, economic, social, dietary, religious, and linguistic background -- has real meaning and biomedical consequences when studying health outcomes.

But despite the need to design research studies that allow scientists to catalog and understand the influence of genetic and non-genetic factors on individual and group responses to treatments, the biomedical research community has been unsuccessful in resolving the under-inclusion of women, older adults, and racial and ethnic minorities into clinical research studies, despite many efforts to improve the performance in this area. Among the contributing factors are:

- Mistrust of medical research -- Half of those taking part in a 2005 Harris Interactive survey agreed that participants in clinical studies are taking a gamble with their health (49 percent) or are treated like guinea pigs (46 percent);<sup>6</sup>
- Lengthy and complex consent forms and other clinical trials materials that are difficult to read and are printed only in English;<sup>7</sup>
- Patients not getting referred to available clinical trials because treating physicians are unaware of the studies, fear additional recordkeeping or losing control of the patient's care;<sup>8</sup>
- Vague information about how Medicare, Medicaid and private health insurers reimburse for the routine costs associated with being in a clinical trial;<sup>9</sup>
- Strict inclusion or exclusion eligibility criteria that excludes patients who have co-morbidities, those who speak languages other than English, and subjects over a certain age;<sup>10</sup>
- Insufficient training for institutional review boards (IRBs), which result in the systematic approval of research protocols that do not provide for inclusion of underrepresented populations;

Divergent federal policies about the level of participation of racial and ethnic groups in government-sponsored clinical trials; and

- A significant duplication of effort in the diseases studied by government and private industry sponsors, resulting in insufficient attention and resources for diseases, such as liver and kidney cancers, where there are significant disparities in outcomes and high-case fatality rates.

Because the stakes are so high, the Chronic Disease Prevention and Control Research Center (CDPCRC) at Baylor College of Medicine in Houston and the Intercultural Cancer Council (ICC) initiated the EDICT (Eliminating Disparities in Clinical Trials) Initiative, a multi-year process funded by Genentech, Inc. to review relevant policies of public, private and non-profit sponsors of clinical trials to identify problems and prescribe solutions.

Involving more than 300 public health officials, medical researchers, and patient advocates who worked in teams over several years, the EDICT review led to the recognition that a coordinated approach is needed to design and fund clinical trials. This will entail implementing a series of practical and realizable policy solutions to clinical trials disparities at the federal, state and institutional levels in the public, private and non-profit sectors as follows:

1. **Implement regulatory changes to improve the way research trials are designed and conducted** Although federally-sponsored clinical trials are covered by the NIH Revitalization Act of 1993, which mandates the inclusion of women and minorities as subjects of federally-funded clinical research, government guidelines has not translated into measurable improvements. According to numerous studies and reports, clinical trials are still falling short of appropriate inclusion percentages.<sup>11</sup> Further complicating the problem, the policies of the Food and Drug Administration -- which oversees the research conducted to bring new drugs and devices to the market -- are not aligned with the NIH. Addressing these discrepancies and expanding the application of the federal government's CLAS (Culturally and Linguistically Appropriate Services) standards in clinical trials are necessary steps to improve the way government-sponsored research is designed and conducted.
2. **Increase the collaboration between government and industry in the design and implementation of clinical research.** Because nearly 75 percent of the funding for clinical trials comes from corporate sponsors,<sup>12</sup> new initiatives that attract more women, older people, minorities, and rural populations into research studies are needed to ensure the generalization of results. This will entail creating new regulatory incentives for pharmaceutical industry trials to include underrepresented populations, as well as imposing penalties for non-compliance with federal policy on appropriate inclusion.
3. **Foster community involvement in clinical trials.** Today, community organizations are usually left out of the clinical trials process, resulting in increased costs and additional resources for investigators to conduct population-relevant clinical trials and secure enrollment into these trials. Towards this end, the EDICT team recommends that investigators build a detailed plan for community engagement into the research protocol that includes demonstrated methods and measures for working with community organizations and institutions.

4. **Implement new policies so that peer-reviewed medical/science journals address the issue of the representation of trial subjects in clinical research studies.** Although peer-reviewed medical/science journals have addressed significant issues where increased attention by the scientific community is warranted, the discussion of diversity, inclusion and representation in clinical trials has been missing from published studies.<sup>13</sup> To change this situation, the EDICT team is calling on two chief editorial organizations for biomedical publications -- the International Committee of Medical Journal Editors (ICJME) and the World Association of Medical Editors (WAME) -- to adopt standards that require investigators to include in their manuscripts an analysis of how the subject population's demographics correspond to those of the population that bears the greatest disease burden.
5. **Invest in specialized training for Institutional Review Boards.** Although the mission of institutional review boards (IRBs) is to safeguard the rights, safety, and well being of all trial subjects, IRB members often lack the training needed to recognize how disparities manifest themselves in research protocols. Thus, IRBs regularly approve research protocols that do not provide for inclusion of under-represented populations. Accordingly, an important priority is to work through the HHS Office of Human Research Protections (OHRP), which oversees the regulation of IRBs, and the Association for the Accreditation of Human Protections Programs (AAHRPP) to add specific requirements that IRBs receive training in healthcare disparities.
6. **Reallocate research funding to avoid duplication and address disparities.** Because government, non-profit and industry sponsors often conduct medical studies on the same diseases,<sup>14</sup> there is a duplication of research efforts in some disease categories and insufficient attention and resources for diseases, such as liver and kidney cancers, where there are significant disparities in outcomes and high case fatality rates.<sup>15</sup> Addressing this problem will require an honest broker to access areas of duplicative research, which is why EDICT recommends that the Institute of Medicine conduct a new study that will recommend strategies for eliminating duplication and promoting coordination. Based on this assessment, Congress will be able to ensure that federal research funding complements private sector funding and gives priority to diseases with the greatest disparities and the highest case fatality rates.

7. **Enhance public education about clinical trials.** Lack of awareness about clinical trials and fear or mistrust of medical research remains pervasive obstacles to patient accrual.<sup>16</sup> Moreover, the complexity of consent forms and other clinical trials materials is often a barrier for those patients with low health literacy<sup>17</sup> -- the inability of an individual to access, understand and use health-related information and services to make appropriate health decisions. Accordingly, advocates recommend widespread development and implementation of culturally appropriate recruitment and retention plans with an additional focus on community education provided in appropriate languages for non-English and limited-English speaking populations.
8. **Implement participant navigation as a critical element of the clinical trials process.** Modeled after the "navigator" program created at Harlem Hospital, patient navigation is a new tool that helps patients keep their appointments and solves their non-medical problems. Because of its potential to retain patients in medical research studies, an analogous process termed "participant navigation" should become the accepted standard of practice for institutions conducting clinical trials.
9. **Assure insurance coverage of the costs associated with clinical trials.** The costs associated with participating in a clinical trial are a concern to all patients and have remained a major barrier to patient accrual. While some private health insurance companies cover the routine patient costs of participating in a research study, this policy is far from universal and often is not made explicit. Further complicating the situation are existing Medicaid policies, which while implemented by the states, do not have universal standards for covering clinical trials participation and the confusion about Medicare procedures and standards for coverage. Addressing these issues will entail actions by both policy makers and the business community to identify and close any existing gaps and to produce and disseminate easy-to-understand information about what the insurance program actually covers.

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Everyone in the health care system -- from patients and caregivers to treating physicians, payors, research scientists, and policy makers -- has a significant role to play in increasing access to quality health care. Thus, an agenda that removes the barriers to clinical trial participation and advances education and information sharing is a critical step to improving the health status of all Americans. Clearly, the time for action is now.

## **Introduction**

Arguably, clinical trials were first introduced in *The Canon of Medicine* in 1020, when the Muslim physician, scientist and theologian Ibn Sīnā, whose Latinized name was Avicenna, laid down rules for the experimental use and testing of drugs and wrote a precise guide for practical experimentation in the process of discovering and proving the effectiveness of medical therapies.<sup>18</sup> Today, scientists use the same process to conduct thousands of clinical trials each year at hospitals, universities, doctors' offices, and community clinics across the country.

Whether funded by government agencies, non-profit sponsors, or the pharmaceutical and medical device industries, clinical trials fall into five different categories:<sup>19</sup> 1) treatment trials, which test experimental treatments, new combinations of drugs, or new

approaches to surgery or radiation therapy; 2) prevention trials that look for better ways to prevent disease in people who have never had the disease or to prevent a disease from returning; 3) diagnostic trials, which are conducted to find better tests or procedures for diagnosing a particular disease or condition; 4) screening trials to test the best way to detect certain diseases or health conditions; and 5) quality of life or supportive trials, intended to identify ways to improve the comfort and the quality of life for individuals with a chronic illness.

But while clinical trials are a critical resource for the discovery of new prevention, diagnostic and treatment methods for disabling diseases, the sad fact is that very few Americans actually take part in these research studies. According to the latest data available:

- Although an estimated 80,000 clinical trials are conducted every year in the U.S., only 2.3 million Americans participate in these studies. This is less than one percent of the entire U.S. population;<sup>20</sup>
- Looking specifically at cancer clinical trials where a lot has been published about the composition of clinical trials, only about 3 percent to 5 percent of the 10.1 million adults with cancer in the U.S. participate in cancer clinical trials;<sup>21</sup>
- When it comes to the makeup of clinical trials, the National Institutes of Health requires that women and members of minority groups be included in all NIH-supported biomedical and behavioral research projects involving human subjects. Despite this requirement, little measurable improvement has been made in increasing clinical trials participation in such populations;
- Of those participating in cancer clinical trials, under-representation among adults aged 65 and over is a major concern. Using 2003 data, researchers found that while 61 percent of all cancer cases occur in older Americans, only 25 percent of the participants in national clinical trials were over 65 years of age.<sup>22</sup> Moreover, in Phase II and III clinical trials, older Americans carried 60 percent of the disease burden but represented only 32 percent of enrolled patients.
- Moreover, the lack of participation of older adults in clinical trials extends to many illnesses that are associated with aging, such as Alzheimer's disease,<sup>23</sup> arthritis,<sup>24</sup> and incontinence.<sup>25</sup>
- At the same time, adolescents are often under-represented in clinical trials. Again looking at cancer clinical trials, only 10 percent of all 15-to-19 year old cancer patients are entered into clinical trials compared to 60 percent of those under age 15;<sup>26</sup>

- The problem is equally acute among women, although differences in the sexes affect the prevalence and severity of a broad range of diseases, including cancer. According to a study published in *Cancer Causes and Control*, as of 2006, no studies examined the impact of sexual orientation on recruitment of women to breast cancer clinical trials;<sup>27</sup>
- Among those who participated in clinical trials to test new cancer drugs between 1995-1999, less than 10 percent collectively represented African Americans, Asian/Pacific Islanders, Hispanics and Native Americans, according to an FDA review;<sup>28</sup>
- American Indians and Alaska Natives who have less than a college degree are rarely included in any type of cancer clinical trials.<sup>29</sup>

While disturbing, these statistics only begin to demonstrate the magnitude and scope of the problem. According to one study published in 2003 by the Tufts Center for the Study of Drug Development, the fully capitalized cost to develop a new drug averages \$897 million.<sup>30</sup> However, if the studies testing these new agents don't adequately represent the patient population, unforeseen safety problems may become apparent after the drug is already marketed, possibly resulting in increased morbidity and mortality for certain patients. This proved to be the case at the end of the 1990's, when eight in ten of the prescription drugs pulled from the U.S. market were found to pose greater health risks for women than men.<sup>31</sup>

Under-representation of specific populations in clinical trials is also at direct odds with the current state of medical science and drug discovery. With the successful sequencing of the human genome, scientists are faced with the new challenge of documenting, describing and understanding the non-random pattern of human genetic variation and its link to disease risk in different patient groups. Findings from the large amount of genetic data generated to date show that more than 90 percent of the observed genetic variations occur within rather than between groups.<sup>32</sup> This underscores the fact the ethnicity -- which incorporates multiple variables including genetics, economic, social, dietary, religious, and linguistic background -- has biomedical consequences when studying health outcomes.

From the perspective of developing better and more targeted therapies, the future of medicine will be based on research design strategies that allow scientists to catalog and understand the influence of genetic and non-genetic factors on individual and group responses to treatments.

### **A Time for Action**

Clearly, there is no dearth of concern about what has been highlighted for years as a singular, serious problem: inadequate accrual of patients that are most representative of the diseases being studied into clinical trials.

For more than two decades, research on accrual deficiencies has continued with increasing specification, looking to explain reasons for the absence of improvement despite many years of calls for expanded participation. And the findings all point to the same conclusions: more clinical trials and more involved physicians are needed; co-morbidities and other ineligibility requirements that minimize generalization of results and that exclude older patients demand reassessment; and more physicians need to be persuaded to present trial options for patients' consideration.

But despite this general assessment, the deficiencies in the way clinical trials are designed, carried out and funded in the U.S. have received little direct, systematic, or sustained intervention. Compounding the situation, the limited collaboration between the federal government and the pharmaceutical industry about research priorities has led to major gaps in research priorities, especially for diseases, such as liver and kidney cancers, that feature high disparities and high-case fatality rates. This fragmented approach to resource allocation leaves many populations under-represented in clinical trials, especially those who bear a disproportionate burden of disease.

At the same time, divergent federal policies about the level of participation of under-represented groups in research studies has led to confusion among the scientific community with the result that many women and other populations remain under-represented in government and industry funded clinical trials. Addressing this problem will require a common vocabulary that is generally accepted and can be widely adopted as well as additional oversight from the National Institutes of Health to enforce existing federal laws covering NIH-funded clinical trials.

Because the consequences are so great, the EDICT team recognized the need for a coordinated approach to designing and funding clinical trials built upon the essential tenants of the EDICT credo:

- Everyone should have the opportunity and necessary support to participate voluntarily in clinical trials for which they are eligible.
- Participants and researchers should understand the benefits of diversity in clinical trials.
- Results from clinical research should benefit the participants' communities and society at large.

Reinforcing these principles, the National Institutes of Health and a number of voluntary health organizations focusing on the major chronic diseases have weighed in with policy statements about the need to include both sexes and a diverse sampling of racial and ethnic groups in clinical trials. The consensus of these groups is that reducing the barriers to clinical trial participation by women, older Americans, and under-represented populations is essential to the drug discovery process. As stated in the *NIH Policy and Guidelines on The Inclusion of Women and Minorities as Subjects in Clinical Research* as amended in October, 2001:

“Since a primary aim of research is to provide scientific evidence leading to a change in health policy or standard of care, it is imperative to determine whether the intervention or therapy being studied affects women or men or members of minority groups and their subpopulations differently.”<sup>33</sup>

Further elevating the need for action are professional organizations, such as the Endocrine Society, whose members are directly impacted by the direction and pace of the drug discovery process. As summarized in an a white paper on increasing minority participation in clinical research, the Endocrine Society stated that clinical trial data that is not based on studies with appropriate representation cannot be presumed to be applicable to “all the key ethnic minorities who suffer a higher burden of these diseases . . . .”<sup>34</sup> The position paper also makes clear, “Scientifically, it makes no sense to develop new treatments among populations of patients who are different from those who will be using them.”<sup>35</sup>

Despite this recognition, however, the EDICT review concludes that extensive barriers to clinical trial participation exist at every level, requiring immediate and longer-term policy change. Towards this end, the EDICT team identified nine distinct areas of causality, viewing these root causes as opportunities for policy change. These nine areas are:

1. Allocation of research dollars;
2. Insurance coverage for costs associated with clinical trials;
3. Professional education;
4. Public education;
5. Community participation;
6. Participant navigation;
7. Industry sponsorship;
8. Publications; and
9. Regulatory climate.

But because these barriers require major systems change, the EDICT team designated nine “opportunity teams” to catalogue the most significant barriers to participation, examine current policies related to clinical trials, and identify opportunities for policy change around each topic area. This analysis was then honed down to six broad categories where stakeholders have direct lines of influence and can make meaningful change:

1. Sponsors/Funders of Clinical Trials
2. Researchers – Clinical Trials Protocols or Design
3. Researchers – Professional Education and Publications
4. Community – Participation
5. Participants – Insurance
6. Participants – Support

With these six categories as the basis, the EDICT team applied a rigorous process of discussion groups, web-facilitated meetings and national conference calls to develop a series of practical and realizable policy solutions to clinical trial disparities at the federal, state and institutional levels in the public, private and non-profit sectors. Before issuing these recommendations, the EDICT team went through successive waves of internal and targeted external review, and initiated a formal public comment period, with survey software designed to

facilitate such comment. This feedback was incorporated into the final set of policy solutions outlined in this report.

While no single strategy will guarantee adequate representation by all populations in prevention and treatment trials, taking targeted and incremental steps will significantly reduce the disparities that are keeping many Americans -- especially women, the elderly, racial/ethnic minorities, those who are low income, and those living in rural areas -- from participating in these studies. *This report, therefore, is intended as a nationwide call to action.* Everyone in the health care system – from patients and caregivers to treating physicians, payors, research scientists, and policy makers – has a significant role to play in increasing access to quality health care. Thus, an agenda that removes the barriers to clinical trial participation and advances education and information sharing is a critical step to improving the health status of all Americans. Clearly, the time for action is now.

## **What Is Behind Disparities in Clinical Trials: Human Factors That Contribute to the Problem**

Although the United States is becoming more diverse, the biomedical research community has been unsuccessful in resolving the under inclusion of women, older adults, and racial and ethnic minorities into clinical research studies, despite many efforts to improve the performance in this area. Why? A number of inter-related human factors influence the attitudes and motivations of the patients who are needed for clinical trials, the physicians that treat these individuals, and the scientists who design and conduct the studies. The following describes these factors and the challenges they represent.

### **Public Attitudes Towards Clinical Trials**

The accrual of adequate numbers of people to participate in medical research studies is an ongoing problem for biomedical researchers. Although the general public has come to expect and demand that the biomedical community develop new, safe and effective approaches to the prevention and treatment of diseases, research has shown that most Americans are unaware of clinical trials as an option or are misinformed about the clinical trials process.<sup>36</sup>

According to Harris Interactive®, which has surveyed the general public about the importance of clinical trials since 2001, most adults agree that people who participate in clinical research studies are making a contribution to science (86 percent in 2005) and are part of an experiment to test experimental medications/treatments not already available to the public (79 percent).

But Harris Interactive also finds the majority of Americans have doubts about the safety of clinical trials. In the 2005 survey, half of respondents agreed that participants in clinical studies are taking a gamble with their health (49 percent) or are treated like guinea pigs (46 percent). When asked specifically about these risks, the public sees the greatest risk as experiencing possible side effects (47 percent).

Reinforcing these findings is a smaller survey of people living in Southwestern Pennsylvania. Published in 2000 in the *Journal of Health & Social Policy*<sup>37</sup>, this telephone survey of 489 adults measured the willingness of these individuals to take part in a medical research study and the factors contributing to their decision, such as their health status, demographic characteristics, attitudes and beliefs about participation, and their knowledge about the conduct of medical research. Similar to the Harris Interactive findings, this survey found only half of those polled (46 percent) said they would be willing to take part in a medical research study focusing on a new treatment for a specific disease, whereas 25 percent stated that they would not be willing and another 29 percent said they were undecided about participating.

At the same time, the findings from an “awareness and willingness survey” of cancer patients and their families living in Southern California finds a significant association between those who are “knowledgeable” and their “willingness to participate” in a cancer clinical trial.<sup>38</sup> However, regardless of their degree of knowledge, racial and ethnic minorities and those aged 18-24 years reported being more reluctant to participate.

Taken together, these opinion surveys document a major perception gap among the public about the importance of participating in a clinical trial. Moreover, because nearly two in five (38 percent) adults say the media is their main source of information about clinical research,<sup>39</sup> public controversy over the potentially dangerous side effects of certain prescription drugs and, on a larger scale, more coverage of clinical studies in general can negatively affect public perceptions. Therefore, new education initiatives that promote public understanding about the importance and benefits of clinical trials are essential to overcoming the public’s mistrust about participating in medical research.

### **Patient-Related Factors**

When it comes to clinical trials, a number of barriers keep many women, older patients, racial and ethnic minorities and those living in rural areas from participating in health research. One of the most obvious and yet challenging is patient awareness. According to a landmark survey of 6,000 cancer patients conducted in 2000, more than eight in ten respondents (85 percent) said they didn’t consider being in a clinical trial because they were unaware that participation might be an option.<sup>40</sup> However, when learning about the possibility, most expressed interest in being in the clinical trial because they would have more care and attention.

The same survey of cancer patients, however, uncovered some pervasive concerns about clinical trials that keep patients from choosing to participate. When patients were asked what would keep them from enrolling in a clinical study, the most common reason was the belief that the standard treatment is better (37 percent), followed by fear of getting a placebo instead of actual treatment (31 percent), and fear of being treated like a guinea pig (21 percent). The belief that insurance will not cover treatment is another major concern cited by cancer patients (20 percent).<sup>41</sup>

While these concerns are pervasive among patients, a recent report by the Agency for Healthcare Research and Quality (AHRQ) -- *Knowledge and Access to Information on Recruitment of Underrepresented Populations to Cancer Clinical Trials* -- finds mistrust of research and research institutions among African Americans and other minority populations is a frequently reported barrier to participating in clinical trials.<sup>42</sup> In fact, a random survey of 717 outpatients at 13 cardiology and general medicine clinics in Maryland conducted by researchers at Johns Hopkins University and reported in early 2008 found only 27 percent of African Americans would agree to enroll in a mock trial to test a new heart disease therapy compared with 39 percent of the white patients. Of those who declined, 72 percent of black patients said doctors would use them guinea pigs without their consent, versus 49 percent of whites.

Fear and mistrust of medical research are also commonplace within the Latino/Hispanic population, especially among those who are undocumented and may sense an anti-immigrant sentiment and fear of deportation.<sup>43</sup> At the same time, people from different cultural

backgrounds may have views that differ from Western medicine. As a result, some beliefs regarding health and disease – including views regarding alternative medicine, the use of traditional healers, religion and prayer – may make participation in clinical trials a less desirable option.<sup>44</sup>

While these barriers remain significant, public health officials are increasingly concerned about those obstacles that prevent willing patients from participating in clinical trials. For example, many U.S. clinical trials require English proficiency for potential participants, automatically excluding those who have difficulty speaking and reading English.<sup>45</sup> According to the Robert Wood Johnson Foundation, an estimated 20 million people in America --about one in every 15 people -- fall into this category,<sup>46</sup> including more than 8 million Latino immigrants with limited English proficiency.<sup>47</sup>

Even when English is not a problem, the complexity of consent forms and other clinical trials materials may be a barrier for those patients with low health literacy -- the inability of an individual to access, understand and use health-related information and services to make appropriate health decisions. As a case in point, the initial consent form for the STAR trial, a national breast cancer prevention trial, was over eight pages long and required a 10<sup>th</sup> grade reading level.<sup>48</sup>

Low health literacy is a special problem for many older adults who are often less likely to want to participate in clinical trials because of the daunting consent process, and multiple forms that need to be signed.<sup>49</sup> Research reported in 2000 showed that older Americans suffer from worse functional health literacy overall, even when factors such as visual acuity, chronic medical conditions, and health status are taken into account.<sup>50</sup> Further, a study reported in 1999 found that 44 percent of adults aged 65 and older scored at the lowest reading level -- and that health materials, such as consent forms and medical information brochures, are often written at levels exceeding their reading skills.<sup>51</sup>

Compounding these problems are concerns about the costs of participating in clinical trials and practical issues, such as transportation to and from the trial site and being able to take time off from work to manage family responsibilities.<sup>52</sup> Even when participants have insurance, some health maintenance organizations require co-payments when patients are enrolled in a clinical trial.<sup>53</sup> Among those without health insurance, a study of National Cancer Institute (NCI)-sponsored cancer treatment trials found that uninsured patients represented only 5.4 percent of all clinical trial participants.<sup>54</sup>

## Physician-Related Factors

For many patients, one of the biggest stumbling blocks to taking part in a medical research study is the advice of their doctor. According to the 2005 survey conducted by Harris Interactive, more than one-quarter (27 percent) of those who participated in a study said their physician was their main influence in deciding to participate. Additionally, 79 percent of respondents who indicated a willingness to participate in a clinical research study said they would be very or somewhat likely to check with their regular physician first.

Added to this opinion research, AHRQ's systematic review of the literature reveals a direct correlation between provider attitudes and accrual to health research studies. Specifically, AHRQ identified nine studies that demonstrate how provider attitudes and perceptions affected enrollment in cancer clinical trials. Four studies found provider attitudes as a barrier to enrollment<sup>55</sup> while one study found provider attitudes to be a promoter of patient accrual.<sup>56</sup>

What AHRQ and other research bodies have also found is that many physicians are reluctant to engage in referral.<sup>57</sup> Why? According to AHRQ's assessment, physician decisions are based on a number of factors, including the patient's age, co-morbidity issues, disease stage, mistrust of researchers, and lack of physician awareness about available trials.<sup>58</sup> Adding to these concerns, many physicians also fear losing control of the patient's care or consider the introduction of patient management protocols as a territorial restriction of their practice rights.<sup>59</sup> Further, some physicians worry that referring patients to clinical trials will increase their paperwork and record keeping, resulting in an excessive administrative or financial burden to their practice.<sup>60</sup>

Addressing these concerns first requires the recognition that the treating physician and other healthcare professionals are an essential link between patients and the research community conducting clinical research. Thus, community practitioners must be brought into the clinical trials loop, so they will know what studies are taking place in their localities.

Engaging community-based health professionals in the clinical trials process also necessitates a significant investment in professional education, starting in medical and nursing school. Currently, little to no information about how clinical trials are conducted is incorporated into continuing medical education programs (CME) offered to physicians. For example, neither the Accrediting Council for Continuing Medical Education (ACCME), nor the American Academy of Family Physicians (AAFP), which maintains a separate CME accreditation process for family physicians, specifically address issues related to diversity or disparities in clinical trial recruitment. However, nothing precludes raising these issues in appropriate CME contexts.

At the same time, formal research training -- especially clinical research training -- is scant in medical education curricula, and medical schools' curricula that address health care disparities are frequently limited and offered as electives. It is not surprising then that when the Accreditation Council for Graduate Medical Education (ACGME) endorsed general competencies for residency training in 1999, the organization did not include specific requirements for training in understanding and interpreting research.

To fill this troubling education gap will require developing a curriculum that will allow medical students to understand the medical research process and the need to increase proportionate representation in clinical trials. Curricula should be designed to produce graduates with sufficient

knowledge and skills to provide patients with information and counseling about clinical trials.

Expanding the core competencies of clinicians also requires a significant investment in expanding professional education. This can be provided through courses offered by recognized medical sub-specialty and allied health organizations as well as incorporating materials into existing ACGME tools that teach Core Competencies.

### **Investigator Barriers**

Persuading physicians to broach the issue of clinical trials more often, as policy makers recommend, would be greatly facilitated by resolving today's physician concerns, including more protocols with fewer eligibility restrictions to facilitate enrollment of additional, more representative patients. However, these restrictions are commonplace. As a result, many racial and ethnic minorities and older Americans are routinely disqualified from participating in clinical trials when their participation would lead to information about the efficacy and safety of new therapies for specific subpopulations.

One recent example is a study of African American cancer patients where only 8.3 percent were eligible for clinical trial participation due to strict eligibility criteria. Nearly 20 percent were excluded due to the presence of additional health problems.<sup>61</sup>

According to the EDICT review, researchers themselves contribute to this problem both in how they design the research protocols and how they recruit patients into clinical studies. Although the sponsor of the study sets the eligibility criteria for clinical trials, many researchers are not proactive in challenging boilerplate language that excludes patients with co-morbidities, those who speak languages other than English, and subjects over a certain age.

Even more troubling is the very real problem of intentional exclusion of racial and ethnic minorities from clinical trials. This was one of the findings of a major study analyzing the enrollment decisions of over 70,000 individuals participating in 20 clinical trials studying both new drug treatments and surgical options.

According to this study, there were substantial differences by race and ethnicity in the number of individuals *invited* to participate. In particular, seven of the 17 clinical and surgical intervention trials offered enrollment to relatively few individuals from minority groups, substantially fewer than would be expected based on the percentage of the population composed of minority groups and the incidence of the diseases being studied.

For instance, the CASS study of surgery versus medical management for angina pectoris offered enrollment to a total of 2,095 individuals, 2,065 of whom were non-Hispanic whites and only 30 of whom were from all minority groups combined. If the study actually reflected U.S. demographics and the higher prevalence of angina pectoris in African Americans and Hispanics, it should have offered enrollment to approximately 356 individuals from minority groups (17 percent of 2,095), more than ten times the 30 individuals from minority groups actually offered enrollment.<sup>62</sup>

As with physician attitudes, the answer to these problems is a greater emphasis on clinical research training programs, which are now mandated for all investigational teams conducting human research trials with federal funding. But despite existing federal regulations, many academic medical centers and research institutions have viewed these requirements as a ceiling rather than a floor. Moreover, the EDICT review finds most supplemental training programs offered to scientists do not address the current state of disparities in clinical trials.

With these discrepancies in mind, the EDICT team is calling for new measures that supplement existing training programs with modules specifically designed to ameliorate disparities in clinical trials. Because clinical research educational programs are so widespread, they represent attractive sites for introducing educational requirements and learning objectives related to disparities in clinical trials.

Another important strategy that will help researchers recruit more patients in medically underserved communities is to bring more minority scientists into mainstream research. Unfortunately, however, 2005 data show that minorities collectively represent less than 10 percent of the U.S. medical school faculty who have an M.D. or Ph.D.<sup>63</sup> Accordingly, more resources are needed for programs that enhance the research capacity at minority colleges and universities, such as the National Center for Research Resources' (NCRR) Research Centers in Minority Institutions (RCMI) program.

## **What Is Behind Disparities in Clinical Trials: The Institutional Barriers to Better Representation**

Even as the biomedical research community focuses increased attention to addressing the deficiencies in the design and funding of clinical research, the scope and multi-faceted nature of the problem has significantly clouded the debate.

Besides a general lack of awareness among patients and physicians about the benefits of participating in clinical trials, factors contributing to the problem include a duplication of effort by government and industry research efforts, insufficient attention and resources for diseases, such as liver and kidney cancers, confusing IRB requirements, and the inconsistent interpretation of federal policies and other regulations. The following explains these institutional barriers and how they combine to impede clinical research.

### **A Duplication of Effort**

Although clinical research is essential for scientific discovery and improved therapies, conducting large-scale, multi-center clinical trials requires significant resources. Thus, a critical question asked by the EDICT team is how are the resources of the different research sponsors -- government, non-profit organizations and industry -- being applied? And more importantly, are the funding decisions of these research sponsors leading to major gaps in research for specific diseases where the burden of disease is especially high?

Looking at how medical research is financed in the U.S., previous reviews find that nearly 75 percent of the funding for clinical trials comes from corporate sponsors.<sup>64</sup> Clinical trials make up the largest portion of the \$266 million to \$802 million it is estimated to cost pharmaceutical companies to bring each new drug to market.<sup>65</sup> In addition, scientists employed by pharmaceutical companies play an important role in evaluating the efficacy, safety, and cost-effectiveness of new drugs.

But since economic decisions dictate the funding decisions of the private sector, an important question to ask is how is the other 25 percent of the research funding being allocated? Here, the focus must be on the National Institutes of Health (NIH), which is the single largest sponsor of federal research. Given that the mission of the NIH is "to uncover new knowledge that will lead to better health for everyone," it should come as no surprise that there is intense interest in how NIH sets its research priorities and allocates its sizable budget.

Unfortunately, however, how NIH sets its research priorities is often influenced by political pressure. This was documented in a 1998 study by an Institute of Medicine, *Scientific Opportunities and Public Needs: Improving Priority Setting and Public Input at NIH*,<sup>66</sup> which found that NIH often spends more on diseases that claim fewer lives or cost the healthcare system less in morbidity and mortality. A major reason is the political pressure from disease-specific interest groups,<sup>67</sup> which have been successful in urging Congress to set aside specific amounts by disease or to boost the funding for the Institute that supports most of the research on their disease.

As a consequence, NIH often invests resources in the same diseases as industry and non-profit research sponsors, with the result that there is a duplication of research effort in some disease categories and insufficient attention and resources for diseases, such as liver and kidney cancers, where there are significant disparities in outcomes and high case fatality rates.

To address these shortcomings, the 1998 IOM report advocated that NIH apply the following criteria when determining research allocations:

- The number of people who have a particular disease;
- The number of deaths caused by a disease;
- The degree of disability produced by a disease;
- The degree to which a disease cuts short a normal, productive, comfortable life;
- The economic and social costs of a disease; and
- The need to act rapidly to control the spread of a disease.

However, now that federal funding for NIH-sponsored research is flat or actually decreasing, another important criterion should be to reduce costly duplication of efforts so the federal research dollars -- now estimated at \$97 per person<sup>68</sup> -- are focused on low incidence/high-case fatality/high disparity diseases where allocating public monies is essential to reduce major disparities in care.

This will require an honest broker to access areas of duplicative research, which is why EDICT recommends that the Institute of Medicine conduct a new study that will recommend strategies for eliminating duplication and promoting coordination. In terms of the future of biomedical research, this investment is well worth the cost.

### **Divergent Federal Policies**

Improving the way in which clinical research is conducted is predicated on supportive government policies. However, a number of federal policies may actually contribute to deficiencies in the way research trials are designed and conducted.

One glaring problem is the NIH Revitalization Act of 1993, which mandates the inclusion of women and minorities as subjects of federally funded clinical research. But although NIH issued this policy in 1994 and then amended its guidelines in 2001, the law has not translated into measurable improvements. According to numerous studies and reports, clinical trials are still falling short of their target inclusion percentages. For example, a review conducted by the Food and Drug Administration (FDA) of 493,000 subjects enrolled in 2,581 clinical trials from 1995 to 1999 found the proportion of women fluctuated each year, ranging from 42 percent in 1995 to 55 percent in 1998, with no directional trend.<sup>69</sup>

Moreover, a recent study that followed 235 consecutive African-American patients with cancer who were considered for recruitment onto cancer treatment clinical trials between January 1, 2001 and December 31, 2002 found only 8.5 percent were eligible to participate in these trials and of this number, only 60 percent actually enrolled in these studies. Co-morbidities excluded 17 percent of the 235 patients and advanced disease made an additional 10 percent ineligible. In addition, the presence of HIV or anemia rendered an additional 37 percent of the patients ineligible.<sup>70</sup>

Besides the continued problem of under-represented populations in government-funded clinical trials, another problem is lack of follow up by the appropriate government reviewers after the NIH Institutes approve submitted plans. Addressing these deficiencies is crucial and requires making important changes to the NIH Revitalization Act so that NIH policies are clarified and there is more specific guidance on how to implement appropriate inclusion plans. Another option worthy of discussion is building in incentives for investigators to implement appropriate inclusion plans. This could take the form of scoring grant proposals based on their inclusion strategies.

Further complicating the problems for the research community, the policies of the Food and Drug Administration -- which oversees the research conducted to bring new drugs and devices to the market -- are not aligned with the NIH. Although the FDA issued new guidelines in 2005, the agency views the NIH as the sole agency responsible for addressing disparities in clinical trials. As a result, the FDA does not evaluate whether a clinical trial is inclusive of women or other underrepresented groups in its approval process for new medications.

Another challenge for the research community is the limited application of the federal government's CLAS (Culturally and Linguistically Appropriate Services) standards in clinical trials. Published by the Department of Health and Human Services' (DHHS) Office of Minority Health (OMH) in 2000,<sup>71</sup> these 14 CLAS standards are designed to help healthcare organizations, health practitioners and research institutions make the clinical setting more culturally and linguistically accessible. Of special significance for the design and conduct of clinical research, these standards specifically address language access services, the diversity of staffing, and maintaining a current demographic, cultural, and epidemiological profile of the community for purposes of recruiting and retaining representative participants in clinical trials.

Because greater recognition and application of the CLAS standards have the potential to improve how clinical studies are designed and carried out in local communities, an intensified effort to is needed to drive awareness and adoption of the CLAS standards in clinical research. This will

entail formal training programs for research scientists as well as written policies and clinical research guidelines that specifically address CLAS standards as part of the study design.

### **Insufficient Training for Institutional Review Boards**

Before any study involving human subjects can be conducted in the U.S., research institutions are required to appoint an institutional review board (IRB) to perform critical oversight functions that are scientific, ethical, and regulatory. Often referred to as the “gatekeepers” for the conduct of biomedical research, IRBs must approve the research design and protocol, require modifications if necessary, and maintain oversight of the clinical trial to maximize the safety of subjects once they are enrolled in the project.

In this country, IRBs are governed by Title 45 CFR (Code of Federal Regulations) of the National Research Act of 1974,<sup>72</sup> which defines IRBs and requires them for all research that receives funding, directly or indirectly, from federal agencies. Moreover, the Food and Drug Administration mandates IRB review of any clinical trial conducted for the purposes of FDA review.

But while the mission of IRBs is to safeguard the rights, safety, and well being of all trial subjects, IRB members often lack the training needed to recognize how disparities may manifest themselves in research protocols. Thus, IRBs regularly approve research protocols that do not provide for inclusion of under-represented populations. These actions, though unintended, are also counter to the ethical provisions set forth in 1978 in the *Ethical Principles and Guidelines for the Protection of Human Subjects of Research* report, commonly known as the Belmont Report.<sup>73</sup> Specifically, the Belmont report states that research studies must ensure that “reasonable, non-exploitative, and well-considered procedures are administered fairly” among all trial subjects.

Because IRBs play such a critical role in the design of clinical trials, educating the research scientists and ethicists that sit on these committees is essential if IRBs are to pay more attention to the participation of women, older adults and minorities in research studies. This can be accomplished by working through the HHS Office of Human Research Protections (OHRP), which oversees the regulation of IRBs, and the Association for the Accreditation of Human Protections Programs (AAHRPP) to add specific requirements that IRBs receive training in healthcare disparities.

## Concerns about Insurance Coverage

Regardless of how well the study is designed and monitored, the question for many Americans is whether insurance companies will pay the costs to participate in a clinical trial. Although sponsors are required to cover the cost of tests, procedures, drugs, extra doctor visits and any research directly related to the study itself, a major barrier to patient accrual involves reimbursement for routine patient care costs. These costs include the charges that insurance should be expected to cover, such as physician charges, hospital charges, and routine tests. While some private health insurance companies cover these routine costs, the policy is far from universal and often is not made explicit.<sup>74</sup> The impact, according to a survey conducted by the American Society of Clinical Oncology (ASCO) is that denial of reimbursement for routine patient care costs is a major obstacle to enrollment in clinical trials.<sup>75</sup> At the same time, research finds that the ambiguity of what insurance companies cover also discourages patient accrual.<sup>76</sup>

Because of these difficulties, 19 states (Arizona, California, Connecticut, Delaware, Georgia, Illinois, Louisiana, Maine, Maryland, Massachusetts, Missouri, New Hampshire, New Mexico, North Carolina, Rhode Island, Tennessee, Vermont, Virginia and West Virginia) have enacted laws that require health insurance companies to provide coverage for clinical trials.<sup>77</sup> Moreover, in 2000, the Centers for Medicare & Medicaid Services (CMS) authorized Medicare to reimburse the routine patient care costs for clinical trials participation.

But these actions have had limited impact. At the federal level, CMS has reopened discussions about its policies regarding Medicare coverage, stating its intention to further define the process, procedures and standards for coverage. This situation is further complicated by Medicaid policies, which while implemented by the states, do not have universal standards for covering clinical trials participation.

Of equal concern to the public health community is the lack of a consistent policy regarding FDA-approved clinical trials, where much of the cutting-edge research is taking place. To address these gaps, the Cancer Leadership Council, a coalition of cancer advocacy organizations, issued a white paper calling on Congress to pass a Patients' Bill of Rights that includes a clinical trials coverage provision.<sup>78</sup> The CLC also advocates for broadening federal and state clinical trials coverage to include private FDA-approved clinical trials.<sup>79</sup>

While these initiatives are worthy of consideration, they do nothing to address the specific challenge of recruiting under-represented populations into clinical trials. Solving this persistent problem will require new action from CMS to ensure that Medicare beneficiaries receive information explaining the benefits of participating in a clinical trial and the patient costs Medicare will cover. CMS can also play an important role by developing a reporting mechanism to gather and disseminate information on state coverage for clinical trials in Medicaid and SCHIP programs.

At the same time, addressing the concerns of patients covered by private insurance plans will require working with insurance companies to provide more information about the specifics of their coverage and then educating benefit managers that often serve as gatekeepers for employees. In addition, employers have a role to play by pressing insurers to provide coverage

for clinical trials in their healthcare plans.

### **Policies of Medical Journals**

Medical journals aspire to select, through peer review, the highest quality science. Accordingly, the reputations of these publications depend on the trust of all stakeholders -- readers, authors, researchers, reviewers, editors, patients, research subjects, funding agencies, and administrators of public health policy -- in a publication process that is judged to be thorough, objective, and fair. Towards this end, an increasing number of journals now publish their stated policies and make them accessible to their constituents by publishing them in print or on the Web.

Thus, today, medical journals have developed explicit policies addressing the study's design, statistical issues and outcomes, the role of the institutional review board or ethics committee, authorship, peer review, and potential conflicts of interest. All of these are fundamental to the scientific publication process and the dissemination of sound science.

But medical journals also play an influential role in the advancement of science by addressing issues where increased attention by the scientific community is warranted. This was the case in 1966, when Henry Beecher's famous article on ethics and human experimentation detailed research abuses at major academic centers and served as a significant stepping-stone on the path to formal regulation of clinical research.<sup>80</sup> Medical journals have also been at the forefront in advancing such issues as improved reporting practices for clinical trials, policies regarding confidentiality and privacy, and making comparisons between meta-analyses and large trials on the same topic.

As important to the future of science is the issue of the representation of trial subjects in clinical research studies. While there is evidence that populations that bear disproportionate burdens of disease are consistently under-represented in clinical trials, discussions of diversity, inclusion, and representation in clinical trials are rarely reported in published studies. This is unfortunate because a candid, scholarly discussion of disparities in research studies would provide an important learning opportunity both for the study authors and those reading about and discussing the study.

To drive this discussion and debate will require that the leading scientific and medical publications recognize the problems resulting from under-representation of specific patient populations in clinical trials and then address these problems on the grounds of scientific rigor, social justice<sup>81</sup> and regulatory applications. It is hoped that this will ultimately lead to increased awareness among all stakeholders and to new policies that address the need to report clinical research findings according to diversity and inclusion criteria.

### **Disenfranchised Communities**

Authentic community participation, as opposed to representation, in the clinical trials process is rare and compounds the challenges of recruiting patients for research studies that reflect all segments of the population. In most cases, community leaders are recruited after research funding has been secured and only to help recruit patients for the trial.

Beyond community relations, the consequences of this common practice are significant. Not engaging community leaders at the beginning of the process results in a lack of understanding about the dynamics of the community and the cultural and local norms that influence how information about clinical trials is communicated to underserved populations and by whom. It can also lead to distrust about the purposes of the research study and the sponsoring institution. Moreover, when designed in a vacuum, the study may fail to include the infrastructure needed to support residents over the long term. Together, these problems lead to increased costs and additional resources to conduct population-relevant clinical trials and accelerate enrollment into these trials.

To prevent these problems, public health experts advocate a new system of community engagement that:

- Builds on strengths and resources within the community
- Facilitates collaborative, equitable involvement of all partners in all phases of the research
- Integrates knowledge and intervention for mutual benefit of all partners
- Promotes a co-learning and empowering process that attends to social inequalities
- Involves a cyclical and iterative process
- Addresses health from both positive and ecological perspectives
- Disseminates findings and knowledge gained to all partners
- Involves long-term commitment by all partners.<sup>82</sup>

Towards this end, the EDICT team recommends that investigators build a detailed plan for community engagement into the research protocol that includes demonstrated methods and measures for working with community organizations and institutions. At the same time, the EDICT team advocates widespread use of participant<sup>83</sup> navigation, a relatively new concept that helps patients navigate within today's complicated healthcare system so they can participate in a clinical trial. Modeled after the "navigator" program created at Harlem Hospital, participant navigation helps patients keep screening and lab appointments and solves their non-medical problems, such as providing child care services.

## **Improving Clinical Research: An Agenda for Action**

### **Nine Priority Areas for Action**

Mounting evidence shows that there are major deficiencies in the way clinical trials are designed, carried out and funded in the U.S. with serious implications for the outcomes of medical research studies.

Of key significance for the future of scientific innovation is the exclusion or under-representation of women, older people, minorities, and rural in the vast majority of the research studies conducted in the U.S. Without adequate representation of all patient populations, researchers cannot learn about potential differences among groups and cannot ensure the generalization of results.

For more than two decades, research on accrual deficiencies has continued with increasing specification, looking to explain reasons for the absence of improvement despite many years of calls for expanded participation. And the findings all point to the same conclusions: more clinical trials and more involved physicians are needed; co-morbidities and other ineligibility requirements that minimize generalization of results and that exclude older patients demand reassessment; and more physicians need to be persuaded to present trial options for patients' consideration.

But despite this general consensus, the deficiencies in the way clinical trials are designed, carried out and funded in the U.S. have received little direct, systematic, or sustained intervention. Compounding the situation, the limited collaboration between the federal government and the pharmaceutical industry about research priorities has led to major gaps in research priorities, especially for diseases, such as liver and kidney cancers, that feature high disparities and high-case fatality rates.

This fragmented approach to resource allocation leaves many populations under-represented in clinical trials, especially those who bear a disproportionate burden of disease. Moreover, divergent federal policies about the level of participation of women, older adults and racial/ethnic groups in clinical trials has led to confusion among the research community with the result that populations remain under-represented in government and industry funded clinical trials.

Because the stakes are so high, the EDICT (Eliminating Disparities in Clinical Trials) Initiative recognizes the need for a coordinated approach to designing and funding clinical trials and has developed a series of practical and realizable policy solutions to clinical trial disparities at the federal, state and institutional levels in the public, private and non-profit sectors.

To substantially improve the clinical research process, EDICT calls for action in the following areas:

1. **Seek regulatory changes that improve the way research trials are designed and conducted.**

2. Reinvigorating federal policies and regulation related to disparities in clinical trial requires that:

- **The National Institutes of Health (NIH) should** provide more detailed instruction on appropriate inclusion plans for underrepresented populations in clinical trial protocols, with substantial incentives for investigators to implement appropriate inclusion plans.
- **The Food and Drug Administration (FDA) should** harmonize its policy with NIH policy to require appropriate inclusion of underrepresented populations in clinical trials.
- **The Food and Drug Administration (FDA) should** implement penalties for non-compliance with inclusion policies in clinical trials;
- **The Food and Drug Administration (FDA) should** implement incentives for appropriate racial and ethnic inclusion in clinical trials.
- **Federally and privately funded sponsors of clinical trials should** adopt the national standards for Culturally and Linguistically Appropriate Services (CLAS) standards developed by the Department of Health and Human Services' Office of Minority Health (OMH).

3. **Increase collaboration between the government and industry sectors in designing and conducting research studies.**

Because nearly 75 percent of the funding for clinical trials comes from corporate sponsors, new initiatives that attract more women, older people, minorities, and rural populations into research studies are needed to ensure the generalization of results. Accordingly:

- **The pharmaceutical industry should** require investigators to have the subject population include members of underrepresented communities that appropriately correspond to the proportions such communities comprise in the targeted population.
- **The pharmaceutical industry should** select and develop investigators with the capability of achieving appropriate diversity of inclusion based on the population served.
- **The pharmaceutical industry should** require that clinical trial plans take account of how the affected communities will receive information and other benefits as a result of the trial.

4. **Foster community involvement in clinical trials.**

Because disenfranchising communities leads to increased costs and additional resources to conduct population-relevant clinical trials and accelerate enrollment into these trials, new initiatives are needed to create a new system of community engagement. This will require that:

- **Public and private sponsors of clinical trials should** require demonstration in protocols of methods and measures to ensure meaningful community participation throughout the clinical trial process.
- **Public and private sponsors of clinical trials should** require a detailed plan to build community capacity for understanding and supporting clinical research, e.g., ongoing participant navigation programs.
- **Community groups should** develop plans to actively disseminate information on clinical trials to community members.
- **Community groups should** develop ongoing relationships with individual investigators and research institutions to promote meaningful dialogue that ensures community involvement.

5. **Implement new policies so that peer-reviewed medical/science journals address the issue of the representation of trial subjects in clinical research studies.** Although peer-reviewed medical/science journals have played an influential role in the advancement of science by addressing issues where increased attention by the scientific community is warranted, the discussion of diversity, inclusion and representation in clinical trials is often missing from published studies.

Advancing this scholarly discussion about disparities in research studies will require that:

- **The International Committee of Medical Journal Editors (ICJME) and the World Association of Medical Editors (WAME) -- the two chief editorial organizations for biomedical publications -- should** adopt standards that require investigators to include in their manuscripts an analysis of how the subject population's demographics correspond to those of the population that bears the disease burden.

6. **Invest in specialized training for Institutional Review Boards.** Although the mission of institutional review boards (IRBs) is to safeguard the rights, safety, and well being of all trial subjects, IRB members often lack the training needed to recognize how disparities may manifest themselves in research protocols. Thus, IRBs regularly approve research protocols that do not provide for inclusion of underrepresented populations. To change this situation will require that:

- **Institutions that mandate clinical research training should** include modules addressing the existence of disparities and providing practical strategies for ameliorating them.
- **Medical education and graduate medical education (residency) standards should** require education addressing basic principles of clinical research and disparities in clinical trials.
- **Providers of continuing health professional education should** incorporate into their programs education addressing basic principles of clinical research, disparities in clinical trials, and awareness of the importance of CLAS standards.

- **The Association for the Accreditation of Human Research Protection Programs (AAHRPP) should** ensure that Institutional Review Boards (IRBs) receive training in health care disparities in general and disparities in clinical trials.
- **The Office of Human Research Protections (OHRP) in the Department of Health and Human Services (HHS) should** issue policy guidance materials designed to enhance IRBs knowledge as to inclusion of underrepresented populations in clinical trials.

7. **Reallocate research funding to avoid duplication and address disparities.** Because government, non-profit and industry sponsors often conduct medical studies on the same diseases, there is a duplication of research efforts in some disease categories and insufficient attention and resources for diseases, such as liver and kidney cancers, where there are significant disparities in outcomes and high case fatality rates.

Reallocating research funding so it is more effective will require that:

- **Congress should** ensure that federal research funding complements private sector funding, and gives priority to diseases with the greatest disparities and the highest case fatality rates.
- **Congress should** request that the Institute of Medicine conduct a study to investigate duplication of clinical trials funding among public, private, and nonprofit sectors, and recommend strategies for eliminating duplication and promoting coordination.
- **State, municipal, and federal policymakers should** work with states as they implement state health plans in order to increase participation of underrepresented populations in clinical trials.

8. **Enhance public education about clinical trials.** Lack of awareness about clinical trials as a treatment or prevention option and fear and mistrust of medical research remain pervasive obstacles to patient accrual. Moreover, the complexity of consent forms and other clinical trials materials is often a barrier for those patients with low health literacy -- the inability of an individual to access, understand and use health-related information and services to make appropriate health decisions.

Addressing these problems requires that:

- **Public and private sponsors of clinical trials should** require the development and implementation of culturally appropriate recruitment and retention plans with an additional focus on community education provided in appropriate languages for non-English and limited-English speaking populations.
- **Public and private sponsors of clinical trials should** require that all local clinical trial teams convene a community “recruitment and retention” committee to advise on such plans as part of the IRB review.

9. **Implement participant navigation as a critical element of the clinical trials process.** Modeled after the "navigator" program created at Harlem Hospital, participant navigation is a new tool that helps patients keep screening and lab appointments and solves their non-medical problems but is not now an accepted standard of practice for institutions conducting

clinical trials. Thus patient navigation is either an after thought in study design and execution or not used at all. Changing this situation will require that:

- **Institutions and providers of continuing education should** institute basic training in Participant Navigation.
- **Institutions and sponsors of clinical trials should** ensure that entities that conduct clinical trials have the capacity to deliver participant navigation services and encourage research protocols that include specific Participant Navigation plans.

10. **Assure insurance coverage for the costs associated with clinical trials.** The costs associated with participating in a clinical trial are a concern to all patients and have remained a major barrier to patient accrual. While some private health insurance companies cover the routine patient costs of participating in a research study, the policy is far from universal and often is not made explicit. Complicating the problem, many employer benefits managers may lack knowledge to know what the insurance policy covers.

At the same time, federal regulations extending Medicare coverage for patients enrolled in clinical trials has had limited impact. Besides unclear policies defining the procedures and standards for coverage, Medicaid policies, implemented by the states, do not have universal standards for covering clinical trials participation.

To remove these barriers will require action by both the business community and federal policies makers. For the business community, addressing gaps in coverage and information about private health insurance plans requires that:

- **Business groups and associations should** request that their members provide coverage for clinical trials.
- **Employers should** ensure that the coverage is accessible and usable by the employee.
- **Employee benefit or insurance trade groups should** request their members educate benefit managers on clinical trials coverage.

At the federal level, assuring insurance covers the patient costs associated with clinical trials necessitates that:

- **Congress should** expressly authorize Centers for Medicare and Medicaid Services (CMS) to adopt policies linking coverage of costs associated with clinical trials to sponsors' and research teams' certification that the protocol contains specific plans and demonstrated capacity to ensure appropriate inclusion and representation of populations underrepresented in clinical trials.
- **Centers for Medicare and Medicaid Services (CMS) should** develop a reporting mechanism to gather and disseminate information on state coverage for clinical trials in Medicaid and SCHIP.
- **Centers for Medicare and Medicaid Services (CMS) should** encourage Medicaid and SCHIP programs to adopt Medicare standards on clinical trials coverage, and gather and disseminate that information.
- **States mandating clinical trials coverage should** mandate that insurers educate policyholders of coverage status for clinical trials.
- **Centers for Medicare and Medicaid Services (CMS) should** ensure that Medicare

beneficiaries have education and information about clinical trials coverage.

## **The Time is Now**

Creating a public policy agenda that addresses the deficiencies in the way clinical trials are designed, carried out and funded in the U.S. is essential for the discovery of new prevention, diagnostic and treatment methods for disabling diseases. However, because the aspects of the problem are multi-dimensional and involve all stakeholders, meaningful improvements will not occur unless there is a coordinated approach to system change.

Everyone in the health care system – from patients and caregivers to treating physicians, payors, research scientists, and policy makers – has a significant role to play in increasing access to quality health care. Thus, an agenda that removes the barriers to clinical trial participation and advances education and information sharing is a critical step to improving the health status of all Americans. Clearly, the time for action is now.

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<sup>5</sup> See, e.g., Charles N. Rotimi, *Understanding and Using Human Genetic Variation in the Design and Conduct of Biomedical Research*, available at [http://www.bcm.edu/edict/PDF/Scientific\\_Rationale.pdf](http://www.bcm.edu/edict/PDF/Scientific_Rationale.pdf). (last accessed Mar. 25, 2008).

<sup>6</sup> Gullo, K. (2005) New Survey Shows Public Perception of Opportunity to Participate in Clinical Trials Has Decreased Slightly From Last Year. Harris Interactive Healthcare News, Volume, 5 (6). Available from: [http://www.harrisinteractive.com/news/newsletters/healthnews/HI\\_HealthCareNews2005Vol5\\_Iss06.pdf](http://www.harrisinteractive.com/news/newsletters/healthnews/HI_HealthCareNews2005Vol5_Iss06.pdf).

<sup>7</sup> See, e.g., Killien, M., et al., *Involving minority and underrepresented women in clinical trials: the National Centers of Excellence in Women's Health*.9(10) J. WOMEN'S HEALTH AND GENDER BASED MED. 1061 (2000); Nguyen, T.T., C.P. Somkin, and Y. Ma, *Participation of Asian-American women in cancer chemoprevention research: physician perspectives*, . 104(12 Suppl) CANCER 3006 (2005); Giuliano, A.R., et al., *Participation of minorities in cancer research: the influence of structural, cultural, and linguistic factors*, 10(8 Supp.) ANNALS OF EPIDEMIOLOGY S22 (2000).

<sup>8</sup> See Intercultural Cancer Council Network, *Cancer Clinical Trials: Participation by Underrepresented Populations*, available at <http://iccnetwork.org/cancerfacts/cfs11.htm> (last accessed Mar. 25, 2008).

<sup>9</sup> National Cancer Institute. U.S. National Institutes of Health. States that require health plans to cover patient care costs in clinical trials. Retrieved June 22, 2007, from: <http://www.nci.nih.gov/clinicaltrials/developments/laws-about-clinical-trial-costs>

<sup>10</sup> See, e.g., Ford, J.G., et al., *Knowledge and access to information on recruitment of underrepresented populations to cancer clinical trials*, 122 EVIDENCE REPORT: TECHNOLOGY ASSESSMENT (SUMMARY), 1-11 (2005); Adams-Campbell, L.L., et al., *Enrollment of African Americans onto clinical treatment trials: study design barriers*, 22(4) J. CLIN. ONCOLOGY 730 (2004); Gross, C.P., et al., *Enrolling older persons in cancer trials: the effect of sociodemographic, protocol, and recruitment center characteristics*, 23(21) J. CLIN. ONCOLOGY 4755 (2005).

<sup>11</sup> See, e.g., Ford, *supra* note 10; see also ICC Fact Sheet, *supra* note 8 (citing sources).

<sup>12</sup> See, e.g., General Accounting Office, NIH Clinical Trials: Various Factors Affect Patient Participation 1, 4 (1999), available at <http://www.gao.gov/archive/1999/he99182.pdf> (last accessed August 18, 2007); see also Hamilton Moses III, E. Ray Dorsey, David H. Matheson, and Samuel O. Thier, *Financial Anatomy of Biomedical Research*, 294 JAMA 1333, 1335 (2005).

<sup>13</sup> See Endocrine Society White Paper, *White Paper: Increasing Minority Representation in Clinical Trials*, at 3, 8 (2007); available at [http://www.endo-society.org/publicpolicy/health\\_disparities/upload/Final%20Color%20White%20Paper%20with%20Endorsers.pdf](http://www.endo-society.org/publicpolicy/health_disparities/upload/Final%20Color%20White%20Paper%20with%20Endorsers.pdf) (last accessed Mar. 25, 2008); accord Carlos Guevara et al., *Gender, Racial, and Ethnic Disclosure in NIH K-Award Funded Diabetes and Obesity Clinical Trials*, 12(3) ACCOUNTABILITY IN RESEARCH (2006) (finding that out of 165 papers, only 37% disclosed the race of the study participants, and that this percentage did not increase even after the NIH Revitalization Act was enacted in 1993); Jorge G. Burneo & Roy Martin, *Reporting Race-Ethnicity in Epilepsy Clinical Trials*, 5(5) EPILEPSY & BEHAVIOR 743 (2004) (finding that less than 7% of all epilepsy clinical trials reported on the race/ethnicity of study participants, and that less than 2% of such studies tried to analyze possible differences in race/ethnicity);

<sup>14</sup> Andrew A. Toole, *Does Public Scientific Research Complement Industry R&D Investment?* Available at <ftp://ftp.zew.de/pub/zew-docs/dp/dp0575.pdf> (last accessed on March 23, 2008). In this discussion paper, Toole addresses the debate of how much public money should be spent on scientific research and on which areas of research should receive funding by asking whether publicly funded research complements private research and development. He concludes that publicly funded basic research is more complementary and thus more important to private industry than publicly funded clinical research. Even so, Moses, et al., found that 43% of the NIH budget

was allocated to support clinical research in 1994 and increased slightly to 45% by 2004. See Hamilton Moses, et al., *Financial Anatomy of Biomedical Research*, 294 JAMA 1333-1342 (2005).

<sup>15</sup> Jon Kerner, *Barriers to Medically Underserved Peoples Participation and Retention in Clinical Trials*, at 3-4, available at [http://www.bcm.edu/edict/PDF/EDICT\\_Barriers\\_to\\_Clinical\\_Trial\\_Participation.pdf](http://www.bcm.edu/edict/PDF/EDICT_Barriers_to_Clinical_Trial_Participation.pdf) (last accessed Mar. 25, 2007).

<sup>16</sup> Comis, R., et al. A Quantitative Survey of Public Attitudes Towards Cancer Clinical Trials. 2000; Available from: [http://www.cancertrials-help.org/static\\_binary/308-9.pdf](http://www.cancertrials-help.org/static_binary/308-9.pdf); Comis, R.L., et al., *Public attitudes toward participation in cancer clinical trials*, 21(5) J. CLIN. ONCOLOGY 830 (2003); See, e.g., Antronette K. Yancey, Alexander N. Ortega, and Shiriki K. Kumanyika, *Effective Recruitment and Retention of Minority Research Participants*, 27 ANN. REV. PUB. HEALTH 1 (2006) (“Perceptions of trust and mistrust of scientific investigators, of government, and of academic institutions were found to be a central barrier to recruitment, particularly among African Americans”); Gina Moreno-John et al., *Ethnic Minority Older Adults Participating in Clinical Research*, 16(5S) J. AGING & HEALTH 93S-123S (2004); Giselle Corbie-Smith et al., *Attitudes and Beliefs of African Americans Towards Participation in Research*, 14(9) J. GEN. INT. MED. 537 (1999); accord Venus M. Gines, *Why Many Latinas Don’t Participate in Clinical Trials*, available at [http://www.bcm.edu/edict/PDF/Latinas\\_and\\_Clinical\\_Trials.pdf](http://www.bcm.edu/edict/PDF/Latinas_and_Clinical_Trials.pdf) (last accessed Dec. 27, 2007) (discussing the history of unethical research as a basis for the subsequent mistrust with which many Latinas perceive clinical research).

<sup>17</sup> See note 2, *supra*.

<sup>18</sup> Toby E. Huff (2003), *The Rise of Early Modern Science: Islam, China, and the West*, p. 218. Cambridge University Press, ISBN 0521529948.

<sup>19</sup> National Institutes of Health: Understanding Clinical Trials, available at <http://clinicaltrials.gov/ct2/info/understand> (last accessed Mar. 27, 2008).

<sup>20</sup> Association of Clinical Research Professionals, as quoted by The Center for Information and Study of Clinical Research Participation (CISCRP) at: <http://www.ciscrp.org/information/facts.asp>.

<sup>21</sup> National Cancer Institute Cancer Clinical Trials: The Basic Workbook, available at <http://www.nci.nih.gov/clinicaltrials/resources/basicworkbook/page1> (last accessed Mar. 27, 2008).

<sup>22</sup> See note 2, *supra*.

<sup>23</sup> *Id.*

<sup>24</sup> *Id.*

<sup>25</sup> *Id.*

<sup>26</sup> Lewis, J.H., et al., *Participation of patients 65 years of age or older in cancer clinical trials*, 21(7) J. CLIN. ONCOLOGY 1383 (2003). National Cancer Institute: Facts & Figures about Cancer Clinical Trials. Available from: <http://www.cancer.gov/clinicaltrials/facts-and-figures>; Newburger, P.E., D.S. Elfenbein, and L.A. Boxer, *Adolescents with cancer: access to clinical trials and age-appropriate care*, 14(1) CURRENT OPINION IN PEDIATRICS (2002).

<sup>27</sup> See note 4, *supra*.

<sup>28</sup> See note 3, *supra*.

<sup>29</sup> Burhansstipanov L. *Overcoming psycho-social barriers to Native American cancer screening research*. In: *Conference summary: recruitment and retention of minority participants in clinical cancer research*, National Cancer Advisory Board, National Cancer Institute. US Dept of Health and Human Services; 1996. NIH 96-4182. p. 109-27.

<sup>30</sup> DiMasi, JA, et al. *Assessing Claims About the Cost of New Drug Development*. Tufts Center for the Study of Drug Development. Tufts University. 2004.

<sup>31</sup> *Science*, June 10, 2005, as quoted by CISCRP, “101 Facts about Clinical Trials”.

<sup>32</sup> See note 5, *supra*.

<sup>33</sup> <http://grants.nih.gov/grants/guide/notice-files/not94-100.html>

<sup>34</sup> Endocrine Society’s Task Force on Increasing Minority Participation in Clinical Research, White Paper, at 3.

<sup>35</sup> *Id.*

<sup>36</sup> <http://www.harrisinteractive.com/news/allnewsbydate.asp?NewsID=941>

<sup>37</sup> Trauth, JM. Et al. *Public Attitudes Regarding Willingness to Participate in Medical Research Studies*, 12(2) J. HEALTH AND SOC. POL’Y 23 (2000).

- <sup>38</sup> Lara, P.N. *Evaluation of Factors Affecting Awareness of and Willingness to Participate in Cancer Clinical Trials*, 23(36) J. CLIN. ONCOLOGY 9282 (2005).
- <sup>39</sup> <http://www.harrisinteractive.com/news/allnewsbydate.asp?NewsID=941>
- <sup>40</sup> Comis, R. et al. A Qualitative Survey of Public Attitudes Towards Cancer Clinical Trials. 2000
- <sup>41</sup> *Id.*
- <sup>42</sup> See Ford et al., *supra* note 10.
- <sup>43</sup> Cultural Competence in Cancer Care: A Health Care Professional's Passport. 2007.
- <sup>44</sup> National Cancer Institute Cancer Clinical Trials: The Basic Workbook, available at <http://www.nci.nih.gov/clinicaltrials/resources/basicworkbook/page1> (last accessed Mar. 27, 2008).
- <sup>45</sup> See note 2 *supra*.
- <sup>46</sup> Robert Wood Johnson Foundation
- <sup>47</sup> Robert Wood Johnson Foundation
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- <sup>50</sup> Baker, D.W., Gazmarian, J.A., Sudano, J., and Patterson, M., *The association between age and health literacy among elderly persons*, 55 THE JOURNALS OF GERONTOLOGY SERIES B: PSYCHOLOGICAL SCIENCES AND SOCIAL SCIENCES S368–S374 (2000).
- <sup>51</sup> Gazmararian, J.A., Baker, D.W. Williams, M.V., Parker, R.M., Scott, T.L., Green, D.C., Fehrenbach, S.N., Ren, J., and Poplan, J.P., *Health literacy among Medicare enrollees in a managed care organization*, 281(6) JAMA, 545(1999).
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- <sup>53</sup> Goldman, D.P., et al. *Incremental Treatment Costs in National Cancer Institute-Sponsored Clinical Trials*, 289(22) JAMA 2970 (2003).
- <sup>54</sup> Sateren, W.W., et al. *How Sociodemographics, Presence of Oncology Specialists, and Hospital Cancer Programs Affect Accrual to Cancer Treatment Trials*, 20(8) J. CLIN. ONCOLOGY 2109 (2002).
- <sup>55</sup> Paskett ED, et al. *Clinical trial enrollment of rural patients with cancer*, 10(1) CANCER PRACTICE 28 (2002).
- <sup>56</sup> Kemeny MM, et al. *Barriers to clinical trial participation by older women with breast cancer*, 21(12) J. CLIN. ONCOLOGY 2268 (2003).
- <sup>57</sup> Hudson, S.V., D. Momperousse, and H. Leventhal, *Physician perspectives on cancer clinical trials and barriers to minority recruitment*, 12(Supp. 2) CANCER CONTROL, 93 (2005).
- <sup>58</sup> See Ford et al., *supra* note 10.
- <sup>59</sup> See ICC Fact Sheet, *supra* note 8.
- <sup>60</sup> *Id.*
- <sup>61</sup> Adams-Campbell, LL. et al. *Enrollment of African Americans onto Clinical Trials: Study Design Barriers*, 22(4) J. CLIN. ONCOLOGY 730 (2004).
- <sup>62</sup> Wendler, D. et al. *Are Racial and Ethnic Minorities Less Willing to Participate in Health Research?* 3(2) PLOS MEDICINE 0202 (2006). While this study is important inasmuch as it suggests that racial and ethnic minorities are often not asked to participate in clinical studies, it is important to note possible methodological flaws in the meta-analysis due to the extreme heterogeneity of the studies involved, as well as problems in the approach (i.e., assessing racial and ethnic minorities' willingness to participate in clinical research without examining those populations' attitudes towards clinical research).
- <sup>63</sup> U.S. Medical School Faculty, 2005. American Association of Medical Colleges. 2005; Available from: <http://www.aamc.org/data/facultyroster/usmsf05/05table12.pdf>.
- <sup>64</sup> See note 12 *supra*.
- <sup>65</sup> Chopra, SS. *Industry Funding of Clinical Trials: Benefit or Bias?* 290 JAMA 113 (2003).
- <sup>66</sup> Scientific Opportunities and Public Needs: Improving Priority Setting and Public Input at the National Institutes of Health. Institute of Medicine. 1998.
- <sup>67</sup> See, e.g., Rebecca Dresser, "Public Advocacy and Allocation of Federal Funds for Biomedical Research," *The Milbank Quarterly* 77, no. 2 (1999): 257-27; David Resnick, "Setting Biomedical Research Priorities: Justice, Science, and Public Participation," *Kennedy Institute of Ethics Journal* 11 (2001): 181-204.
- <sup>68</sup> Department of Health and Human Services. FY 2007 Budget in Brief.
- <sup>69</sup> See Evelyn et al., *supra* note 2.

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<sup>70</sup> See Adams-Campbell et al., *supra* note 62.

<sup>71</sup> See Office of Minority Health, CLAS Standards, available at <http://www.omhrc.gov/templates/browse.aspx?lvl=2&lvlID=15> (last accessed Mar. 25, 2008).

<sup>72</sup> See 45 C.F.R. § 46 *et seq* (2008).

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<sup>74</sup> NIH clinical trials. Various Factors Affect Patient Participation. Washington, DC: US General Accounting Office; September 1999

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<sup>76</sup> Aaron HJ, et al. EXTENDING MEDICARE REIMBURSEMENT IN CLINICAL TRIALS. Institute of Medicine, National Academy Press; 2000.

<sup>77</sup> See Health Policy Tracking Service and National Conference of State Legislatures: State Clinical Trials Coverage (2006).

<sup>78</sup> See Cancer Leadership Council Policy Issues: Clinical Trials, available at [http://www.cancerleadership.org/policy/clinic\\_privins/index.html](http://www.cancerleadership.org/policy/clinic_privins/index.html) (last accessed Mar. 27, 2008).

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<sup>80</sup> Henry K. Beecher, *Ethics and Clinical Research*, 274 N. ENGL. J. MED. 1354 (1966).

<sup>81</sup> See Dorothy Roberts, *Legal Constraints on the Use of Race in Biomedical Research: Towards A Social Justice Framework*, 34(3) AM. J. L. MED. & ETHICS 526 (2006).

<sup>82</sup> Israel, B., Schulz, A., Parker, E., and Becker A., "Review of community-based research: Assessing partnership approaches to improve public health," *Annual Review of Public Health* 19 (1998): 173-202.

<sup>83</sup> By "participant" we mean someone who participates in any clinical trial, including prevention trials.