

Latino Participation in Cancer Clinical Trials

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Abstract

Minorities are disproportionately under-represented in cancer clinical trials in the United States. This is particularly true with Latino-Americans as they are 14% of the U.S. population, but comprise only 3% of the cancer clinical trial population. Because clinical trials represent viable potential treatment options for cancer patients, this situation represents a restriction in access to care choices for Latinos. Importantly, limited minority participation in clinical trials leads to a paucity of data on the response of racial and ethnic subgroups to certain drug-agents. Pharmacogenomic studies indicate that genetic makeup is a significant determining factor in the response of many drugs used today, validating the importance of a full range of trial population representation.

The reasons for Latino under-representation are multi-factorial, but include particular obstacles of socio-cultural beliefs about health care, diminished social resources, learned helplessness, economic disparity, and language barriers. The NIH Revitalization Act is an attempt to ensure adequate representation in clinical trials in order to draw valid conclusions on sub-population response. Community outreach programs employ cultural competency and community education methodologies to better include Latinos and minorities in cancer clinical trials. **CONCLUSION:** It is a vital interest to reduce barriers to robust Latino and minority participation in cancer clinical trials.

Introduction – Clinical Trials

The clinical trial is an essential piece in the process of identifying new and effective drugs in medicine. In the United States, a new compound must undergo rigorous testing in the clinical trial arena in order to show safety and efficacy for a given patient population. This mechanism is regulated in the U.S. by the Food and Drug Administration (“FDA”), which provides guidance in the development process and makes the ultimate decision about approval to release the new drug-agent for general use.

There are a graduated number of phases of clinical trials through which a compound must pass in order to proceed through the approval process. These phases are represented as phases I through IV.

Phase I clinical trials are generally small studies that test for safety and dosing concerns in volunteers. Phase II trials are generally larger in size, test the drug in patients with a particular disease indication, and make determinations of safety, efficacy, and dosing. Phase III trials are typically large, blinded, randomized, multi-centered, and statistically powered studies in a specific disease population. This is the setting where a new compound is tested for efficacy against either current standard treatment or a placebo. Phase III trials results are a substantive measure that the FDA uses in the determination of safety, efficacy, and applicability to patients. And phase IV studies are post-approval overview – aimed at ascertaining long-term safety and efficacy concerns.

There are considerations in the design of cancer clinical trials compared to other therapeutic areas. First, as cancer can represent a life-threatening disease, the drug-agent or regimen will generally (but not always) be tested against standard care, and not placebo. Second, cancer treatments are often too toxic to justify risk to healthy volunteers.

NIH Revitalization Act

Information on toxicity, efficacy, and differential response captured during the trial process is the primary means through which the FDA makes its recommendations for use. It follows then, that this rigorous process should be comprised of a population that mirrors the population that will be treated. There are fundamental issues of appropriate generalization in applying results to a population that was not included in the original clinical trial population.

Of most practical and immediate concern is that women, historically under-represented minorities, and the elderly are not adequately represented in clinical research. Much emphasis has been placed on this idea in recent years. The Federal government enacted the National Institutes of Health (NIH) Revitalization Act of 1993 in order to address the problem of the under-representation of women and minorities in clinical research. This act mandated that women and minorities be included in clinical trial populations for NIH-funded research. The NIH Revitalization Act stipulates that women and minorities must

be recruited into trials in such numbers so as to provide a “valid analysis” of the effects of the intervention in these subgroups. Valid analysis is defined in the Act as an “unbiased assessment ... [to] yield the correct estimate of the difference in outcome between two groups of subjects.”ⁱ

The spirit of the NIH Revitalization Act aims to provide for enough women and minority patients in clinical trials so that any differences in response to an intervention may be captured during the trial process. Implicitly, this act presupposes that race and gender are viable factors that help determine biomedical response. The acknowledgement of race in particular, is an idea that is steeped in controversy. Such so, that some have even called for the exclusion of race altogether from medicine, claiming that it is an insufficient factor of biomedical outcome.ⁱⁱ Other authors have defended the inclusion of race in medicine as a factor of inquiry for reasons that include the exploration of the differential characteristics of disease, disease treatment response, and distinct genetic traits.ⁱⁱⁱ

Latino Representation in Cancer Clinical Trials

There are currently about 43 million people in the US who identify themselves as Hispanic or Latino.^{iv} Similar to non-Hispanic whites, cancer is the second leading cause of death among Latinos in the U.S., accounting for 20% of all mortality.^{iv} There are, however, significant differences in the types of cancer that afflict Latinos. Whereas the death rates due to the most common cancers (prostate, female breast, colon, and lung) are lower for Latinos versus non-Hispanic whites, the rates are higher for certain more rare cancers such as stomach, liver, cervix, and gallbladder.^{iv}

Latino-Americans and other racial and ethnic minorities tend to receive lower quality of care compared to non-Hispanic whites, even when factors such as socioeconomic status and access to healthcare are controlled for.^{v,vi} Latinos have lower 5-year survival rates when grouped for all cancer sites and are more likely to be diagnosed with a more advanced cancer versus whites.^{iv,vi} Indeed, there is a disparity in cancer health outcomes for Latinos in the U.S. that does not appear to be fully attributable to insurance access or to income. Rather, it appears to be associated with ethnicity alone.

Access to cancer clinical trials for Latinos tracks these matters. A recent study of NCI cancer trials has suggested that the number of trial enrollees relative to estimated U.S. cancer rates were significantly lower for Latinos and African-Americans compared to whites.^{vii} The study demonstrated that though the absolute number of trial participants increased during the research period, the proportion of non-whites in cancer clinical trials declined during this same period.

Though Latinos represent 14% of the U.S. population, they represented only 3.1% of the National Cancer Institute (“NCI”) sponsored trial participants between 1996 and 2002.^{vii} Other studies have confirmed the significantly lower cancer clinical trial participation among Latino adults compared to the percentage incidence in the general population.^{viii} Some authors have argued that the number of minority clinical trial enrollees should not

be employed in comparison to minority population statistics because of the differential incidence rates of cancer among minority groups.^{ix} A larger more recent study of NCI clinical trial participants compared the enrollment fraction of minority groups – which was defined as the number of trial enrollees divided by the estimated U.S. cancer population. This study noted significantly lower enrollment fraction rates for Latinos than for non-Hispanic whites.^{vii}

An analysis of minority representation in clinical trials, including non-NIH sponsored trials, also highlights these differences. A 2001 FDA study including non-government sponsored trials noted an under-representation of minority groups in U.S. clinical trials. Latinos, in particular, were found to be under-represented, comprising only 3% of the total 263,794 clinical trial subjects (for which racial status was available).^x

Other minority groups in the U.S., such as Asian-Americans and African-Americans, also have reduced cancer clinical trial enrollment rates compared to whites.^{vii,viii} Additionally, there are reduced numbers of elderly patients enrolled in trials in contrast to elderly incidence of disease.^{xi}

Social Implications of Minority Access to Cancer Clinical Trials

Ensuring minority access to clinical trials is an aspect of good cancer health care. While it is excessive to equate clinical trial participation per se with quality treatment, it is fair to acknowledge that denial to cancer clinical trials - as an option - clearly diminishes the possibility of full access to quality medical care. And, in cases where the investigational compound is found to have efficacy, this lack of access may represent a failed opportunity.

Clinical trials are experimental, and thus do not represent tried and tested treatment approaches. Nonetheless, a trial often presents an opportunity for an individual patient to receive dedicated and focused provider care. Trial participants are often followed-up and assessed more regularly than in standard care.

Winston Price, M.D. of the National Medical Association has punctuated this point in noting that “racial disparities in access to health care will disappear only when adequate and representative samples of minorities participate in clinical trials.”

Health Information Implications of Minority Trial Participation

Uneven participation in clinical trials represents a lost opportunity to discover the effects of a drug-agent on a minority population. There are well-known cases in pharmacology of the differential response of racial groups to certain drugs. For example, in the treatment of hypertension, African Americans as compared to whites, tend to respond more favorably to diuretics and calcium channel blockers - and less favorably to beta-blocker and ACE-inhibitors.^{xii} Likewise, those of Chinese descent tend to be more

sensitive to the effects of beta-blockers than whites and therefore may require a lower dosage.^{xii}

If there is a reduced minority group representation in clinical trials of a drug, then there will be a paucity of information on how that group responds to the drug. FDA approval is almost uniformly given with respect to disease indication, age, and (sometimes) gender, but not to race. Nonetheless, race may have a significant effect on treatment outcome or treatment risk/benefit. This may be of particular concern in the area of cancer care, where many of the drug-agents offer such a narrow corridor between benefit and harm.

Current FDA guidelines on the required content of an NDA application call for the analysis of subgroups of populations with respect to safety and efficacy only if they are available.^{xi,xiii} The lack of a more robust policy in these areas is clearly reflected in an analysis of drug product labels in the US. One FDA-sponsored study found that, of 185 drug labels for new molecular entities between 1995 and 1999, only 45% made any statement regarding race.^x Included in this 45% group were labels with statements to the effect that no racial subgroup analyses were conducted - or that studies were inadequate to detect any differences between subgroups.

Pharmacogenomics Implications

Never before has the importance of individual genetic make-up in drug therapy received as much attention. Pharmacogenomics, the study of the genetic differences among people and their effect on drug response, has highlighted this significance. This relatively new science has begun to show us that generalization in drug therapy may miss important therapeutic keys. That not all people or genetic sub-groups, will respond in the same manner to a given drug regimen.

The differential ability to metabolize drugs in the body is an area that has been studied with particular rigor. Studies of the family of drug metabolizing enzymes of the liver known as cytochrome P450 demonstrate these differences. One particular family of P450 metabolizing enzymes, known as CYP 2D6, is estimated to play a part in the metabolism of 25% of drugs used today.^{xiv} CYP 2D6 metabolizing ability has been shown to directly correlate to genetic factors.^{xv,xvi} The ability to metabolize drugs, whether poorly or rapidly, directly affects the concentration of drug available in the body to perform its intended pharmacologic function. The proportions of “poor metabolizing” CYP2D6 patients are known to vary significantly based on race. Asian poor metabolizer incidence, for example, is significantly lower in comparison to Caucasians incidence. “Ultra-rapid CYP 2D6 metabolizers”, those individuals with a tremendously rapid ability to metabolize drugs via CYP2D6, are known to be quite rare in Caucasian populations but can represent as much as 29% of Northeastern African communities.^{xvii} In the study of pharmacogenomics, race is an important determinant in predicting response to a drug.

In cancer, minority status has been shown to correlate with poorer survival status.^{xviii} Studies have shown reduced duration of survival in African-American breast cancer patients compared to white patients. This is a finding that was found to correlate to genetic differences between these two populations.^{xix} African-American prostate cancer survival rates have also been shown to be poorer compared to white patients.^{xx} These poorer outcomes among minorities persist even when disease stage at diagnosis are controlled for.

Barriers to trial participation

There are barriers to patient participation in clinical trials. Annually, only 3% of cancer patients participate in NCI-sponsored trials.^{vii} Analyses of these barriers have noted a number of causative factors including those of patient, protocol, and physician-related barriers.^{xxi} Patient-related issues included such matters as quality of life concerns, preference for other treatments, and lack of awareness about the study itself. Protocol-related barriers included unease with randomization, the possibility of receiving a placebo, and the potential of treatment side-effects. Physician-generated issues included the negative impact on the doctor-patient relationship, fear of patient coercion, and the belief that physicians, not external study designs, should make treatment decisions for the patient.^{xxi}

A recent Harris Interactive Survey of 6,000 cancer patients indicated that 85% of patients did not consider participation in a trial because they did not realize that this was an option available to them.^{xxii} Thus, the single greatest barrier to the lack of clinical trial participation may well be the absence of awareness that clinical trials are even an option. Other peer-reviewed survey studies have shown that only 59% of cancer patients, family and friends understood the meaning of the term “clinical trial.”^{xxiii} Analysis of the attitude of American adults has indicated though a limited number of the polled population understood the meaning of the term clinical trial, 38% of cancer patients indicated that they were willing to participate in such a trial.^{xxiv}

Minority groups are represented disproportionately lower in clinical trials in comparison to the non-minority population in the U.S. These groups are faced with special barriers that affect participation in clinical trials. The barriers to participation in trials for minorities are complex and multifaceted, and might be seen as including socio-cultural, economic, research-related, and individual barriers.^{xxv}

Socio-cultural barriers for minority groups include phenomena such as distrust in the healthcare system, different attitudes towards chronic disease and dying, and perceptions of racial discrimination and segregation.^{xxv} These societal factors contribute to a schism between minority patients and U.S. health care providers, thus dampening the communication channel between them. This affects, among other things, the flow of clinical trial information to these groups. There is the historic precedent of mistrust between minority groups and the healthcare system to consider. African-Americans, for example, live in the shadow of the legacy of Tuskegee experiments, where African-

American men were subjected to clinical experimentation without their consent or knowledge. This legacy is often cited as a reason for reluctance in the African-American community towards clinical trial participation.^{xxvi} Current studies of the differences in attitudes towards clinical trials support this, noting a 1.8 times greater fear of biomedical research in African-Americans versus whites.^{xxvii}

Language barriers are a formidable cultural challenge specific for Latino-Americans in the U.S. Nearly 25% of Latino-Americans aged 5 or greater do not speak English fluently.^{iv} This language issue combined with the often complex and daunting trial eligibility and consent process presents a significant barrier to Latino participation in U.S. clinical trials.

Other shortfalls contributing to inequities in healthcare and clinical trial access include a lack of a sense of personal agency in individual minority group members, educational differentials, and cultural competency. These factors collectively reinforce feelings of learned helplessness, fatalism and distrust towards healthcare in minority groups. Cultural values need to be addressed in the healthcare setting in order to better engender trust. For Latino-Americans, values such as family, mutual respect, and the importance of personal over institutional relationships are considered key cultural elements to be incorporated in the provision of healthcare, including the clinical trial.^{iv}

Economic barriers also exist for minority participation in clinical trials. A larger proportion of minorities tend to live in poverty in the U.S. Approximately 22% of Latinos in the US live in poverty compared with 8% of non-Hispanic whites.^{iv} Poorer individuals may have more difficulties with the traveling and with the time constraints that a clinical trial may impose. Lack of health insurance is another barrier. For Latino-Americans, the proportion of people under 65 years of age who report no health insurance coverage is more than twice that of non-Hispanic whites.^{iv} Individuals without healthcare insurance are less likely to have access to an ongoing healthcare provider, and therefore less likely to have reliable access to information about clinical trials as treatment options.

The burden of the cost of clinical trial procedures is an issue. In practice, an industry-sponsored study will generally pay for procedures specific to the study, but will not reimburse for procedures thought to be standard care. Also, third party insurance providers have been reluctant to offer reimbursement for such services, thereby leaving the burden of payment to others. California has made steps to address this matter. In 2002, California passed a law specifically focused on the problem of insurance reimbursement for cancer clinical trials. Senate Bill 37 mandates that cancer patients' third party insurance "shall provide coverage for all routine patient care costs related to the clinical trial if the enrollee's treating physician, who is providing covered health care services to the enrollee under the enrollee's health benefit plan contract, recommends participation in the clinical trial" after determining that participation in the clinical trial has a meaningful potential to benefit the enrollee.^{xxviii} Therefore, any procedure that is not covered by the sponsoring drug manufacturer must be covered by the patient's insurance carrier. Further, the law mandates that MediCal (Medicaid in California) must

also reimburse for cancer clinical trial procedures for its beneficiaries.

Finally, restrictive clinical trial eligibility criteria present a barrier for some minority enrollment. Narrow enrollment criteria, for example, are well known to affect elderly populations. An analysis of NCI cancer clinical trials noted that only 32% of participants were 65 years or older compared to a 61% incidence of cancer in this population.^{xi} Strict protocol entrance restrictions about organ status and overall functional status frequently prevent the elderly from enrolling in clinical trials. Careful relaxation of such stringent criteria would result in an increase in participation of the non-frail elderly in clinical trials, leading to a better understanding of the response to drugs-agents by the elderly.

Community-Focused Initiatives for Change

Community-focused programs have been created in the US to help address the issue of minority under-representation in clinical trials. One NCI-launched initiative, the Minority-Based Community Clinical Oncology Program (MBCCOP), awards healthcare institutions that build clinical trials minority outreach programs for minority populations. A unifying goal for MBCCOP is to reduce racial and ethnic disparities in cancer outcomes by ensuring equal access to new and innovative cancer treatments.^{xxix} In 2007, MBCCOP benefits from information about minority accrual to cancer clinical trials based on a recent pilot project by the Coalition of Cancer Cooperative Groups, the Stronger Hospital of Cook County (Illinois), and Meharry Medical College of Nashville, Tennessee.

Additionally, U.S Government programs have been established to help remedy general inequities in minority care, specifically in cancer care. The National Institutes of Health includes the National Center on Minority Health and Health Disparities. The National Cancer Institute maintains the Center to Reduce Cancer Health Disparities (CRCHD – <http://crchd.cancer.gov/index.html>), in addition to promoting the Special Populations Networks for Cancer Awareness, Research and Training.

Also, academic and non-profit community-based initiatives and prototypes are beginning to arise as a result of the perceived need to increase minority enrollment in cancer clinical trials. One such project is the EDICT program (Eliminating Disparities in Clinical Trials) as overseen by the Baylor College of Medicine and the Intercultural Cancer Council. EDICT is a three-year program in process that will culminate in a “toolkit” and is specifically aimed at increasing Latino, African-American and Asian-American populations in clinical trials in the Houston, Texas area.^{xxx}

Non-profit efforts include those of the Education Network to Advance Cancer Clinical Trials (ENACCT), and the Cancer Patients’ Alliance for Clinical trials (CancerPACT). As funded by the Lance Armstrong Foundation, ENACCT has established pilot programs aimed broadly at inclusion in cancer clinical trials in the cities and areas of Decatur, Illinois; Pierce County, Washington; and Roxbury, Massachusetts.^{xxxi} Similarly,

CancerPACT is an initiative of the Lorenzen Cancer Foundation that is specifically focused on addressing cultural competency in an effort to increase Latino clinical trial participation in Sacramento, California, and in Denver, Colorado.^{xxxii} Through trust building and barrier reduction among patients and medical providers, this program hopes to improve access to cancer clinical trials for Latinos

Conclusions

Minority groups, including Latinos, are under-represented in cancer clinical trials in the U.S. This situation represents not only an inequity in access to health care options, but also precipitates a lack of knowledge of drug response for these specific groups. Barriers to minority enrollment must be addressed in order to dispel these disparities. Community-focused, culturally attentive outreach programs may begin to attend this problem – and to at least begin to accrue information that can lead to more comprehensive solutions.

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