Chapter 12
Overcoming Barriers for Latinos on Cancer Clinical Trials

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Increasing Complexity of Accrual in Clinical Trials for All Populations

The concept of clinical trials has expanded over the years from straightforward drug-based interventional studies to those that recognize the breadth of the human experience. We are now focusing on preventing cancer, expanding research into screening, primary prevention, active prevention, and behavioral modification in ways that would not have been done before. Still clearly concerned about treatment, we are also concerned about symptom control and how to deliver the care itself, as well as with issues of health economics and survivorship such as healthcare outcomes and post-therapy care. Now, with the complexity of clinical trials, testing whether interventions can make a difference relies on rigorous, well-conducted clinical trials to either support the case or, sometimes just as importantly, demonstrate that the intervention does not work.

In the era of individualized medicine, enrolling patients in clinical trials has become much more difficult because of narrowed eligibility criteria, such as the case where patients must have a particular mutation before they can be enrolled. Another issue is the requirement for randomization. The enthusiasm of patients to be randomized has clearly decreased. Availability of information on the Internet means that individuals learn and question more, and for some, the concept of not being able to select their therapy is very uncomfortable. Being in the placebo group is a frightening thought for most patients; if included, it typically has to be for a finite amount of time, with a fair amount of confidence that they will then be able to receive the

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A. G. Ramirez, E. J. Trapido (eds.), *Advancing the Science of Cancer in Latinos*,
https://doi.org/10.1007/978-3-030-29286-7_12

therapy they seek. Another hurdle to recruitment is that there are now many nonexperimental treatment options, so the patient has to weigh the benefits of standard care against the inconvenience of entering a trial. Other barriers to recruitment are that patients may be wary of becoming a guinea pig for research or of taking experimental drugs they fear will have greater toxicity and adverse effects. Also, patients receive a river of information and misinformation daily from the Internet, television, and the lay press that may give them unrealistic expectations for miracle cancer cures.

There is also the issue of expense of participating in a clinical trial. There is the direct standard of care expense, but there are also expenses that are often not considered. For example, is the experimental drug going to be more expensive? Usually the answer is no, but it may be more expensive to be in a clinical trial in other ways. There may be more travel, more time away from work, and more standard of care expenses. A significant barrier may not be a new experimental therapy, but rather the use of standard of care therapies that are in the control arm and would have to be covered. There are clearly also barriers of third-party payers having significant concerns around trials. Some of that is protected through healthcare policy, but not completely.

There are additional barriers to recruiting racial and ethnic minorities from underserved populations. In 2013, Brown et al. conducted semi-structured audio interviews with 22 African American patients who refused to participate in clinical trials in order to gain insights into their perceptions of clinical trials and reasons for refusal [1]. Most participants refused because of fear of treatment-related burdens and fear of adverse effects. Some refused out of mistrust. Many patients and family members misunderstood the purpose and benefits of the clinical trial, and family members were mostly against participation. However, most patients indicated that they would participate if given access to a decision aid and the ability to discuss their concerns with a provider. In other interventions, these researchers found that with sufficient information, patients felt they could overcome some of these barriers. Other barriers they identified include additional patient burden; in addition to the burden of the disease itself, patients reported their reluctance to undergo more testing and more office visits. Lost time at work and trouble finding transportation were cited most often. Also, patients expressed the fear of participating in an "experiment." Frequently, there was a lack of understanding about the benefits of clinical trials; many patients did not understand that they would continue to treat their cancer and receive high-quality care throughout the clinical trial. Also, most patients were frightened about possible side effects from clinical trials, though, in some cases, the effects were the same as those associated with the standard of care.

Barriers That May Disproportionately Impact Latino Patient Enrollment

What are some barriers that may disproportionately affect Latino patient enrollment in clinical trials? In an effort to answer that question, scientists from the Institute for Health Promotion Research and the Mays Cancer Center at UT

Health San Antonio interviewed patients from south Texas who were receiving treatment at the cancer center. This study explored, from the patients' perspective, both promoting factors and barriers to participation in early phase clinical trials [2]. They found that more Latinos than non-Hispanic whites decline early phase clinical trials and were more likely to be concerned with symptom improvement. On the positive side, Latinos surveyed were more concerned that treatment would improve symptoms, decrease hospitalizations, and have the potential for better outcomes than standard of care. Barriers to participation included greater fear of uncertainty over experimental treatment efficacy and poor communication with their doctor and poor understanding of the purpose of the clinical trial. Exploring this further, Ramirez et al. examined if there was an association between the attitudes and practices of Latino physicians and clinical trial participation [3]. They found that Latino physicians were less connected to and saw less value in clinical trials. The authors identified this as an opportunity for education and engagement with physicians to better promote clinical trial recruitment among Latinos. Langford et al. examined eligibility, refusal rates, and clinical trial participation among patients at sites in the National Cancer Institute's Community Cancer Centers Program [4]. One question they asked was whether minorities have a lower rate of enrollment because they have more comorbidities, such as diabetes, obesity, and hypertension. They found that the odds of comorbidity were higher with older age, males, and non-Hispanic blacks, but not for Hispanics. They also found that consent readability was a factor for refusal across the board and that in this community center setting, there were no racial/ethnic differences in clinical trial enrollment.

One recent study examined underrepresentation of Hispanics in clinical trials from the perspective of clinical trial recruiters [5]. They conducted focus groups with professional recruiters and described how to adapt to potential participants' language competency and literacy levels. One issue that emerged is the consent form, the legal document designed to protect the institution but not necessarily to communicate clearly. Additionally, translating the form from English to Spanish does not necessarily enhance understanding; communicating the general concepts is what is needed. It is also important for recruiters to engage in culturally appropriate verbal and non-verbal communication; establish a sense of connection between recruiters and patients; accommodate socioeconomic concerns; adapt to contextual factors; and respond to potential participants' mistrust of medical research.

Are there differences between urban and rural residents in their willingness to participate in a clinical trial? The results of a telephone survey of South Carolina residents showed no significant differences between the two groups [6]. The researchers who performed the study found that distrust and fear of clinical trials were barriers in both groups. However, clinical trial participation is lower among the rural population, and they attribute this to perceive limited access to clinical trials and a greater lack of knowledge about clinical trials.

Strategies to Facilitate Clinical Trial Participation

How do we augment the enrollment of Latinos into cancer clinical trials? And why do we want to do so? The answer is that cancer clinical trials must reflect the population that we are studying, so that we can capture differences among ethnic groups and make inferences that are generalizable. We (Hispanics/Latinos) may be different in how we process drugs, the genetic profile of disease, or the risk factors we possess. For example, Hispanics/Latinos in the United States have a higher rate and worse outcomes of acute lymphoblastic leukemia than the general population. Why is this so? Do they have a worse molecular profile? Do they have worse cytogenetics? Are they more likely to develop neutropenic fever? If they develop neutropenic fever, are they more likely to take longer to go into the hospital? Do they have more port infections because they do not have family members who are able to assist them with their port? Really delving into these issues is the key to understanding.

An active area of research is determining how to improve accrual into clinical trials. Drs. Iruku and Kaklamani from UC Health Colorado Springs and UT Health San Antonio, respectively, are developing a predictive model of trial accrual. Based on an analysis of 297 trials carried out at the Mays Cancer Center in San Antonio (formerly the CTRC), they found that certain variables—the type of sponsor, author of the trial, and the type of intervention—were significantly associated with accrual. Trials that were observational, interventional, industry-sponsored, and authored by the local PI were more likely to meet accrual goals.

Experience has taught us that it is important for staff involved in clinical trials to be knowledgeable about the study and to have a strong stake in the trial. Having staff such as the nurses, cancer navigators, or clinical trial coordinators who understand the settings around the studies is incredibly important. Dr. Vanessa Sheppard reports a similar approach used at the Massey Cancer Center at Virginia Commonwealth University. Their strategy to improve trial accrual includes using dedicated resource specialists; clinical social workers help patients identify resources, including alternative transportation grants, childcare, or legal assistance, freeing the clinical research nurses to better focus on patient care and treatment. There is also a dedicated insurance authorization coordinator who explains insurance policies to determine coverage and financial obligations. Further, Massey offers communications training not only to physicians but also to nurses. Our experience has been that appropriate communications are important even in terms of the discussion between the infusion nurses or the pharmacy and the patients as well. How one phrases something might have a very significant impact on patients. Finally, another strategy that Massey uses to improve accrual is to build awareness of clinical trials through marketing; it actively promotes its trials in clinics, at community events and within the larger health system.

Enhancing accrual and addressing underrepresentation in clinical trials begin with the process of matching patients with appropriate trials. Our experience is that we are much more likely to have a successful discussion around trials if patients have the preconceived notion that a clinical trial is something positive and that the

physician is someone who might be able to connect them with a study that helps. Determining eligibility is a necessary step to minimize bias in the results from the clinical trial, but it can be a tedious, slow process. Penberthy et al. from the Massey Cancer Center at Virginia Commonwealth University have attempted to automate the process by using matching software; when patients register they can be potentially matched up with a clinical trial [7]. Not only does the automated process reduce the time for eligibility screening, but it also assures patients that there might be a clinical trial for them. The earlier in the process patients become aware that clinical trials are available and might be beneficial, the more likely they are to participate.

At the Mays Cancer Center, we have the mandate to decrease the burden of cancer in our catchment area, which is from San Antonio down to the border. It is a sizable area that is 69% Hispanic, 24% non-Hispanic white, 4% African-American, and 3% other. Our collective efforts reflect this largely Hispanic population, which includes developing a minority recruitment plan for cancer clinical trials. How did we do this? Our first step was to identify the potential resources. A Minority Clinical Trial Accrual Committee was established to try to reduce barriers for accrual and to implement strategies to enhance minority recruitment. A Coordinator of Minority Programs was hired to oversee these activities, which included developing a minority accrual plan required for all clinical trials. As part of this effort, Trevino et al. developed a toolbox to help investigators create a minority recruitment plan and meet those goals [8]. Barriers to minority enrollment were identified through research, focus groups, interviews, and physician outreach. Strategies and materials were then developed including virtual connections with physicians in remote areas in South Texas; Spanish translations of signs, brochures, and consent forms; and expanded media outreach with Spanish-language television (Univision), a Spanish-language daily newspaper in San Antonio (La Prensa), and others. The minority accrual plan (MAP) toolbox thus includes activities that build awareness and improve health literacy. Since its inception in 2013, this group has helped at least 50 clinical trials per year with the goal of improving enrollment in cancer clinical trials. Prior to its implementation, the enrollment of Hispanics into our interventional studies was 46%; now it is 56%. Accrual of Hispanics into interventional non-treatment studies has fluctuated over the years, but in 2017 it was 59%. If we look at non-intervention, observational ancillary-correlative studies, the accrual numbers are lower (37% in 2017). Even within our own Latino communities, when therapy is taken out of the equation, interest in participation wanes. We must communicate better how important the biospecimen study is to inform future research, even though it does not center on immediate therapy.

A research team from the Institute for Health Promotion Research and the Mays Cancer Center at UT Health San Antonio conducted a pilot study to test whether CHOICES, a bilingual multi-component intervention, would empower Latina patients with breast cancer to make informed decisions about clinical trials [9]. The CHOICES intervention included an educational interactive video, a low-literacy booklet, and care coordination by a patient navigator. This randomized controlled study compared the CHOICES intervention group with a control group that received

general clinical trial information. They found that the intervention was more effective than the control in increasing patients' perception of understanding clinical trials and their consideration of a clinical trial as a treatment option.

Next Steps

In conclusion, key opportunities for increasing accrual of Hispanics/Latinos in clinical trials include the education of registering physicians to better promote enrollment in clinical trials. It also includes building general awareness among Hispanic/Latino populations of the role of clinical trials in improving cancer care. The more that it becomes the collective impression, the more successful accrual will be. For example, only a minority of adult patients with cancer goes into clinical trials, but there is a very different experience that exists with pediatric patients. In the pediatric world, it has become by culture, from physicians, staff, and parents that clinical trials are the standard of care for their disease. Almost all patients go into clinical trials; they have been incredibly successful, making great advances in pediatric cancer research. If we can accomplish a similar culture among Hispanic/Latino patients that clinical trials are considered to be a good thing, accrual should improve. Another opportunity to increase accrual is enhancing care navigation to better support the role of cancer clinical trials in treatment planning, including matching up the right patient with the right study. Clearly the issue of language and culture cannot be overstated; there must be language- and culture-appropriate materials, education, and clinical trial coordination. Finally, a key opportunity exists in the sharing of lessons learned between centers and investigators committed to this mission.

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