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Clinical Trials – The Art of Enrollment

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Abstract

Objectives—Enrollment barriers and multidisciplinary approaches to increase cancer trials participation are presented. Recruitment barriers, research in Maryland, and a Best Practice for cancer trials are discussed.

Data Sources—Journal and research articles, web sites.

Conclusion—Clinical trials have produced prevention and care advances for cancer and other diseases. Trial enrollment is lower for minorities and underserved communities. A comprehensive program for addressing enrollment barriers should incorporate research on barriers, multidisciplinary teams, and education and trial infrastructure in community settings.

Implications for Nursing Practice—Health disparities training, including culturally appropriate enrollment approaches for education and retention of underserved communities, should incorporate community stakeholders and nurse/physician researchers.

Keywords

clinical trials enrollment; barriers; accrual; minority and underserved

Clinical trials have produced advances in disease prevention, treatment and rehabilitation for many diseases, including cancer.^{1,2} While the proportion of cancer patients participating in trials generally is low, enrollment is even lower for racial/ethnic minorities and rural communities. Federal policies and national and local educational initiatives have supported programs and research mandates for assuring diversity in clinical trials participation, yet lower participation of racial/ethnic minorities and underserved patients in clinical trials continues to exist.^{2,3,4,5} Assuring diversity in clinical trials enrollment is essential for eliminating health disparities as low enrollment and participation of racial/ethnic minorities

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and underserved patients affects the generalizability of research results for these groups. This is related to not only new drug development but also behavioral or psychosocial interventions. Without enrollment of populations who experience significant disparities in health, treatment and survival improvements are impeded for underrepresented communities.

Cancer Clinical Trial Participation

An estimated 1.4 million new cancers are expected to be diagnosed in the United States (US) in 2008 and over 565,000 deaths are projected.⁶ Despite the significant contributions that clinical trials make to cancer therapy as well as prevention, clinical trial participation for the general cancer patient population is low, between 5-9%.^{1, 2, 4} While federal legislation, regulatory efforts and research initiatives were undertaken to understand and improve diversity in trial accrual⁷, African Americans, rural, and underserved cancer patients continue to participate in cancer clinical trials at lower rates than the general population.^{1, 3, 5, 8, 9, 10, 11} Recent reports of unexplained trends in enrollment are a major concern, as they show that the percentage of African Americans who participate in clinical trials is declining.⁴

Several programs have been developed to foster increased public and health professional awareness and education on trials. Strategies to increase accrual have been guided, in some studies, by research on trial barriers and predictive factors. Efforts to increase the availability of trials, as well as coverage of trial costs, are being implemented to determine if this will increase access to and likelihood of participation in clinical trials by underserved patients. Recent reports also focus on policy implications and the role of state legislation in addressing access to, reimbursement for and participation in clinical trials.

Factors Associated with Trial Enrollment, Particularly for African Americans and Other Underrepresented Populations

Barriers to clinical research participation can occur on multiple levels. A few examples of these levels of influence on trial participation are detailed in Table 1 and include the following: patient factors, health care professional factors, research and investigator factors, as well as structural and community factors. Each can impede participation and retention to clinical trials and are briefly discussed below.

Multiple **patient factors** influence the decision to participate in trials. There is limited access to information on available trials by the general public¹² as well as a lack of understanding and knowledge of the role of clinical research in the development of behavioral interventions or drug development. Additionally the potential benefits and risks of participating in clinical trials are issues supported by national and state surveys on this topic⁸. Existing attitudes toward research, including mistrust of researchers or research institutions and fear, influence patient participation.^{8, 12} Cultural and religious beliefs as well as practical issues, such as having more pressing life concerns (i.e. provision of food and shelter for family), concerns about costs^{4, 13}, and being non-English speaking directly impact patients' enrollment in clinical trials as well.

Health care professionals

report having limited information on available clinical trials as well as how to access such trials for their patients.⁸ Lack of information on how to access trials⁴, lack of awareness of basic trial design requirements such as use of randomization, group assignment, placebo use, types of clinical trials and phases, methodologies and reporting requirements⁸, and lack of basic knowledge of the role of clinical research in improving health⁸ impacts physician

referral and patient accrual. Distrust of academic institutions by community health professionals and concern about losing patients or control over patient care are legitimate concerns and can result in lack of patient referral to clinical trials^{2,12}. Finally, burdensome administrative requirements, paperwork and the lack of administrative support and reimbursement concerns influence referral of patients to trials by community physicians.^{2,14}

Factors related to researchers and investigators

include failure to recognize the importance of utilizing culturally tailored approaches for accrual and retention¹⁵ and failure to recognize fear or distrust of academic institutions and researchers by patients and underserved communities. Lack of cultural competence and communications training of study personnel to explain complex research protocol information to low literate patients, those with limited English ability or non-English speakers impact accrual^{13,15}. Further, training in health disparities and training of researchers to develop the skills needed to foster public trust in research, culture and health disparities is essential to foster diversity in clinical trials. Failure to implement participatory research related to patient enrollment strategies with communities which experience health disparities can perpetuate distrust, as can poor verbal and literacy appropriate communication skills.^{13,15}

Structural or organizational factors

include inconvenient times for clinical trial appointments and other logistical arrangements that are deterrents to accrual for working poor or hourly wage earners who cannot take off work to attend trial follow up visits during business hours. Flexibility with follow up visits to allow appointments in the evening or on weekends is important. Lack of adequate support for community outreach by trial sponsors, including provision of convenient transportation in urban and rural communities, can be a significant barrier⁴. The tremendous outreach costs and supportive resources needed to engage and retain underserved communities in clinical research are often not adequately provided.⁴

Insufficient community based infrastructure and trial design factors¹⁶ are important factors

The National Summit Series on Clinical Trials has worked over ten years and addresses trial design, regulatory and availability of open protocols.¹⁶ Given that the majority of trials historically are conducted within academic institutions, the National Cancer Institute (NCI) has supported conducting trials in community-based settings. NCI-funded programs such as the Community Clinical Oncology Program (CCOPs), Minority-Based (MB) CCOPs, and the Cancer Trials Support Unit (CTSU) have increased community based and primary care participation in cancer control and therapeutic trials sponsored by NCI.^{17, 18}

Historical factors, unethical and exploitative research

The Tuskegee Syphilis Study continues to play a role in shaping public and community attitudes toward research and lack of public trust in research. The US Public Health Service, in 1932, initiated a study to observe the natural history of syphilis involving African American men.^{19, 20, 21} Called the “Tuskegee Study of Untreated Syphilis in the Negro Male”, the study initially involved 600 black men - 399 with syphilis and 201 without the disease. Patient informed consent was not provided to study enrollees who were falsely told by the research team that they were actually being treated for “bad blood,” the term used at that time to describe a variety of health conditions such as syphilis, anemia, and fatigue. Despite availability, patients did not receive appropriate treatment required to cure their disease. Study participants were provided free medical examinations, meals, and burial insurance. The original study period was about 6 years, but it continued for about 40 years.¹⁹

In July 1972, an Associated Press story about the study led the US Assistant Secretary for Health and Scientific Affairs to appoint an Ad Hoc Advisory Panel to review the study. Some of the significant findings of the panel included the following:

- Study participants agreed freely to be examined and treated.
- Researchers had not provided information on the actual purpose of the study, and participants were deceived and were not provided informed consent.
- There was no evidence that study enrollees were provided choice of withdrawing from the study even after penicillin, the treatment of choice early during the study, became available.
- The risk from participation in this study far outweighed the minimal knowledge gained from the study.

Adequate treatment was never offered or provided to the men by the research team despite the recognition of penicillin as the treatment of choice for syphilis in 1947. The study was stopped in November 1972.¹⁹

The Centers for Disease Control and Prevention was given responsibility for the program, where it remains today in the National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention. Widows, children and grandchildren are receiving medical and health benefits. (See Table II.) The consequences of this study are inestimable as it continues to leave a persistent legacy of justifiable distrust of research and the federal government by African Americans in particular.¹⁹

Underestimation of Community Interest in Research

Some reports inaccurately suggest that there is lack of interest in research participation by African Americans and other minorities. Data from our surveys and other studies in Maryland indicate that blacks and other communities which are underrepresented in research are not asked to participate at the same rate as whites, yet they are very interested in research, advances in health and disease management. Blacks report being interested in participating in research if they are provided detailed information on why the study is being conducted, how long it is, and when the results will be provided to them. Blacks also reported in our studies to want information on the amount of time required to participate in medical studies and whether healthcare is being provided. Clear and literacy appropriate communication between the potential clinical trial enrollees, underserved communities and researchers is cited as an imperative by blacks.^{2, 5, 22}

Maryland Approaches

In Maryland, a multilevel approach was developed and implemented to address barriers that exist for patients, health professionals, and at community or structural levels. The University of Maryland School of Medicine (UMSOM) conducted extensive qualitative and quantitative research on clinical trial enrollment barriers to guide the development of programs and strategies to remove these barriers. This includes engagement of various stakeholders and levels of community, as well as leveraging funding to invest in community based trial infrastructure.

Research on Trial Enrollment Barriers and Predictive Factors

A study previously reported in Cancer Detection and Prevention presented barriers to clinical trial enrollment and factors which are predictive of trial participation.⁵ A random digit survey (n=5,154) was conducted by the UMSOM Center for Health Policy and Health

Services Research. The survey examined health status, clinical trials barriers, health care access, and cancer screening in Maryland residents residing in 13 jurisdictions between December 2001 and March 2003. Respondents included English-speaking, non-institutionalized male and female respondents age 18 and older who resided in urban Baltimore City, rural Western Maryland, or the rural Eastern Shore. The questionnaire included questions about clinical trials, including trial barriers and predictive factors, attitudes and information channels.^{5,22}

Over 85% of responders, regardless of race and residence, reported not ever hearing about clinical trials from their physicians.⁵ Of 574 respondents in 13 jurisdictions in Maryland, 11.1% reported *previous recruitment* into clinical trials. Of those, 59.4% reported actual participation in clinical trials. Overall, respondents who were significantly more likely to be recruited were in poor health (OR=1.83, CI=1.21-2.76), had public health insurance coverage (OR=1.98, CI=1.57-2.51), and had some college or higher level of education (OR=2.31, CI=1.84-2.92). Respondents who were significantly less likely to be recruited were black (OR=0.61, CI=0.44-0.85), residents of rural Western Maryland (OR=0.46, CI=0.33-0.65), and residents of rural Eastern Shore (OR=0.30, CI=0.22-0.40).⁵

Respondents who were significantly more likely to actually participate in clinical trials were informed about clinical trials by a health care provider (OR=1.69, CI=1.08-2.65), were knowledgeable about clinical trials (OR=2.09, CI=1.26-3.46), and were able to make the time commitment to participate (OR=1.67, CI=1.06-2.63). Respondents who were less likely to participate in clinical trials were black (OR=0.38, CI=0.21-0.68) or middle-income respondents (OR=0.57, CI=0.37-0.89).⁵

Results of studies on specific barriers are being used to develop educational programs for community health professionals, training for nurse and physician research personnel and for widespread public education on the role of clinical research in community health.

Maryland Programs on Community Based Clinical Trials

A number of federal, state and private grants have supported a comprehensive Maryland approach for fostering enrollment in community based cancer clinical trials.

Maryland Special Populations Cancer Research Network

The Maryland Special Populations Cancer Research Network (MSPN) (grant no:U01 CA86249) was established in 2000-2005 to foster cancer awareness and increased cancer disparities research by establishing collaborative relationships with the communities and community clinicians in Maryland. The MSPN established academic and clinical partnerships to support enhanced minority and rural patient enrollment in cancer prevention, survivorship, and treatment trials, as well as to promote training opportunities for minority researchers and students.²³ The community clinical trial program was initiated through this grant, which led to the HHS National Best Practice Award. Partnerships to foster increased awareness on trials with ministers, community based nurses and physicians were developed. The program was designed to include community and health professional education, via infrastructure incorporating full time nurse clinical research coordinator and nurse community educator, and other infrastructure costs.²⁴

The Maryland Regional Community Network Program

The Maryland Regional Community Network Program (MRCN) was funded in 2005 by the National Cancer Institute at the conclusion of MSPN (grant number U01 CA114650). The Maryland Regional Community Network Program's signed Memorandums of Understanding (MOUs) with community leaders and organizations include a focus on Institutional Review

Board (IRB) and Health Insurance Portability and Accountability Act (HIPAA) training, certification and maintenance of up to date annual certification.²⁵

University of Maryland Statewide Health Network (UMSHN)

The Maryland Statewide Health Network (UMSHN) is a regional and statewide, community-based infrastructure established in 2000 with funding from Maryland's Cigarette Restitution Fund (CRF) Program to promote a broad range of prevention and control activities on cancer and other tobacco-related diseases (Baquet, PI). The UMSHN aims are: 1) to reduce morbidity and mortality of cancer and other tobacco related diseases; and 2) to reduce or eliminate disparities in cancer deaths attributable to racial/ethnic, cultural, geographic, or socioeconomic barriers. In addition to supporting prevention, evidence-based best-practices and community-faculty outreach and research, the UMSHN specifically provides education and seeks to increase participation in clinical trials, within the state and especially in underserved rural and urban areas. This unique, community-based infrastructure consists of a central office in Baltimore City on the University of Maryland (UMB) campus and three regional community outreach offices that are spread over four geographic regions and cover 16 jurisdictions (Baltimore City, rural Eastern Shore, rural Southern Maryland, and rural Western Maryland). UMSHN's regional offices have established community-based partnerships with local health departments, Parish Nurses, community hospitals, community and faith-based organizations, and local coalitions on cancer, tobacco, and other tobacco-related diseases, which enable access to available resources within specific communities and bring together key stakeholders to strengthen and combine health promotion and disease prevention strategies.

UMSHN uses a multi-level approach to increase awareness and participation of diverse populations in clinical trials. This includes provider education through nurse continuing education (CE) and physician continuing medical education (CME) programs; ongoing public/community education, promotion of specific prevention trials to appropriate groups; the development and distribution of clinical trial fact sheets to participants attending community programs and events; and infrastructure support in the form of full time support for nurse Clinical Research Associates (CRAs) for required regulatory and data collection and reporting and nurse community educators.²⁶

Educational programs provided by UMSHN include Parish Nurse continuing education for rural Western Maryland and Mini-Medical School programs, a free 4-6 week educational program on health and disease topics selected by the general public that has graduates across Maryland. These programs focus on demystifying and destigmatizing health, medical information and research for underserved communities. In addition to detailed information about new methods of treating, diagnosing and preventing diseases, curriculum for this program includes education on clinical trials and can include training in human subjects' research, HIPAA, patient privacy training and providing certificates for completion. In addition, a list of questions are provided to participants on "what to ask" if approached by an investigator about trial participation.²⁶

Patient Navigation Pilot Research Study (CRF AND CNP supported)

A pilot randomized control trial of an educational intervention delivered by Community Health Workers (CHWs). The intervention is being evaluated to increase cancer screening behavior. It includes rigorous and ongoing training of CHWs in human subject protections, patient privacy and HIPAA compliance, Tuskegee Study and other historical factors, barriers to clinical research for African Americans and rural underserved communities. Training modules and clinical follow up as well as adherence to protocol is conducted by a

multidisciplinary team including Dr. Baquet, a nurse clinician, research coordinator, research investigators, and outreach staff of UMSOM.

Discussion

Community-Academic Partnerships: A Comprehensive Clinical Trials Model

Our program has implemented comprehensive research to understand existing attitudes and potential barriers to participation and targeted community-based participatory programs to improve accrual of underserved populations to clinical trials. Through local and regional initiatives undertaken with long-standing community partners, an intensive, multi-level program to increase cancer trial accrual and availability in minority and rural underserved communities has been implemented. This comprehensive research and programmatic initiative has resulted in dramatic increases in clinical trials accrual on the Eastern Shore of Maryland, as well as National Best Practice award in 2004 from the US Department of Health and Mental Hygiene.²⁴

An essential component of our programs is health and research literacy and building public trust in research as a tool to eliminate health disparities. UMSOM and Eastern Shore Cancer Research Network implemented a comprehensive model to increase accrual and participation in clinical trials on the Eastern Shore of Maryland. The model has a multi-pronged approach that includes:

- Intensive community education on trial design, benefits and risks,
- Physician and nurse education, and
- Infrastructure for trial regulatory and data collection and management in community rather than academic settings.²⁴

The National Best Practice Award on Rural Cancer Clinical Trials US HHS

The UMSOM Office of Policy and Planning and the Eastern Shore Cancer Research Network, a single community oncologist practice located on the Eastern Shore of Maryland, shared a National Best Practice award from the Secretary of the US Department of Health and Human Services (DHHS) Committee on Science and Policy in September 2004 for increasing Eastern Shore resident access to and participation in cancer clinical trials. The Eastern Shore Cancer Research Network, a community oncologist practice, was an equal partner in this program and award. Between 2000-2006, enrollment in clinical trials on the Eastern Shore of Maryland increased twenty fold and the number of open protocols increased forty fold.²⁴

This is the only clinical trials community centered best practice in the nation and the only rural clinical trial best practice in the nation.

Conclusions

Despite persistent underrepresentation in clinical research of African Americans and other racial/ethnic minorities and underserved communities, there is great interest by these communities in participating in the research process and making societal contributions through research on improvements in health, disease management, and prevention. The art of enrollment in clinical trials requires a comprehensive and multidisciplinary approach to address the persistent effects of historical examples of unethical research and barriers to research participation on multiple levels. Incorporation of community and health professional education, training on culturally competence and health disparities for researchers and policies which support availability of trials and design factors is essential.

Engagement of communities in participatory programs on enrollment and retention of African Americans and other underrepresented groups is important to ensure diversity in trial enrollment.

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Table I

Selected Examples of Factors that Impede Participation in Clinical Trials

Barriers to Clinical Trial Participation	Examples
Patient factors or demographics	<ul style="list-style-type: none"> •minority •aging and rural •poor access to care •low socioeconomic status
Patient/Community awareness, trust issues and history	<ul style="list-style-type: none"> •mistrust of research / medical system •fear of negative results/effects •historical factors •lack of information on available trials
Physician and researcher barriers	<ul style="list-style-type: none"> •reluctance to refer patients (fear of losing patient) •lack of awareness / knowledge of clinical trials benefits •doctor–patient communications •lack of culturally appropriate researcher training to address patient concerns
Infrastructure, design issues	<ul style="list-style-type: none"> •lack of sufficient number of appropriate clinical trials; •disqualification of patients due to eligibility criteria •lack of sufficient infrastructure to support trials in community settings
Perceived or actual cost barriers	<ul style="list-style-type: none"> •patients may be reluctant to participate due to lack of insurance or fears of additional costs •physicians may be reluctant to refer patients due to real and perceived additional costs •oncologists concern: lack of reimbursement for clinical and research costs (ASCOF)

Source: Baquet CR. The Role of State Legislation and Policy in Addressing Disparities in Clinical Trials. Eliminating Disparities in Clinical Trials (EDICT). http://www.bcm.edu/edict/PDF/State_Legislation.pdf

Table II**Timeline Related to Syphilis Study**

1900	<ul style="list-style-type: none"> •Tuskegee educational experiment gains widespread support. •Rosenwald Fund provides monies to develop schools, factories, businesses, and agriculture.
1926	<ul style="list-style-type: none"> •Health is seen as inhibiting development; major health initiative is started. <ul style="list-style-type: none"> ◦ Syphilis is seen as major health problem. •Prevalence of 35% observed in reproductive age population.
1929	<ul style="list-style-type: none"> •Aggressive treatment approach initiated with mercury and bismuth. <ul style="list-style-type: none"> ◦ Cure rate is less than 30% ◦ Treatment requires months and side effects are toxic, sometimes fatal. •“Wall Street Crash”—economic depression begins.
1931	<ul style="list-style-type: none"> •Rosenwald Fund cuts support to development projects. •Clark and Vondelehr decide to follow men left untreated due to lack of funds in order to show need for treatment program.
1932	<ul style="list-style-type: none"> •Follow-up effort organized into study of 399 men with syphilis and 201 without. <ul style="list-style-type: none"> ◦ The men would be given periodic physical assessments and told they were being treated. •Motin agrees to support study if “Tuskegee gets its full share of the credit” and black professionals are involved (Dr. Dibble and Nurse Rivers assigned to study).
1934	First papers suggest health effects of untreated syphilis.
1936	<ul style="list-style-type: none"> •Major paper published; study criticized because it is not known if men are being treated. •Local physicians asked to assist and asked not to treat men. It was also decided to follow the men until death.
1940	Efforts made to hinder men from getting treatment ordered under the military draft effort.
1945	Penicillin accepted as treatment of choice for syphilis.
1947	<ul style="list-style-type: none"> •USPHS establishes “Rapid Treatment Centers” to treat syphilis. <ul style="list-style-type: none"> ◦ Men in study are not treated, but syphilis declines.
1962	Beginning in 1947, 127 black medical students are rotated through unit doing the study.
1968	Concern was raised about ethics of study by Peter Buxtun and others.
1969	<ul style="list-style-type: none"> •CDC reaffirms need for study and gains local medical societies’ support •AMA and NMA chapters officially support continuation of study.
1972	<ul style="list-style-type: none"> •First news articles condemn studies. •Study ends.
1973	Congress holds hearings and a class-action lawsuit is filed on behalf of study participants.
1974	<ul style="list-style-type: none"> •A \$10 million out-of-court settlement is reached <ul style="list-style-type: none"> ◦ US government promised to give lifetime medical benefits and burial services to all living participants. ◦ The Tuskegee Health Benefit Program (THBP) was established to provide these services.
1975	Wives, widows and offspring were added to the program.
1995	The program was expanded to include health as well as medical benefits.
1997	On May 16 th , President Clinton apologizes on behalf of the Nation.

Source: Centers for Disease Control and Prevention (CDC). The Tuskegee Timeline. Accessed: March 9, 2008; Available at: <http://www.cdc.gov/tuskegee/timeline.htm>