

# Dialogues on Diversifying Clinical Trials



## Successful Strategies for Engaging Women and Minorities in Clinical Trials

The Society for Women's Health Research  
United States Food and Drug Administration Office of Women's Health

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## ABBREVIATIONS

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|         |   |
|---------|---|
| AACT    | African-Americans in Clinical Trials  |
| AAPI    | American Association of Physicians of Indian Origin                             |
| ACTTION | Alliance for Clinical Trial Trustworthiness in Our Neighborhoods                |
| AHT     | American Health Technology  |
| AI      | American Indian   |
| AIAN    | American Indian and Alaska Native   |
| AIDS    | Acquired Immunodeficiency Syndrome  |
| ALLHAT  | Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial     |
| BLA     | Biologic License Application  |
| BMI     | Body Mass Index   |
| BPA     | Bisphenol A   |
| CAB     | Community Advisory Board  |
| CBER    | Center for Biologics Evaluation and Research (FDA)                              |
| CBPR    | Community-based participatory research  |
| CCT     | Cancer Treatment Clinical Trial   |
| CDC     | Centers for Disease Control   |
| CDER    | Center for Drug Evaluation and Research (FDA)                                   |
| CDRH    | Center for Devices and Radiological Health (FDA)                                |
| CED     | Coverage with Evidence Development  |
| CEDRICT | Coalition to Eliminate Disparities and to Research Inclusion in Clinical Trials |
| CHD     | Coronary Heart Disease  |
| CHE     | Center for Health Equity, University of Maryland                                |
| CISCRP  | Center for Information & Study on Clinical Research Participation               |
| CMS     | Centers for Medicare and Medicaid Services                                      |
| CRA     | Clinical Research Association   |
| CRO     | Clinical Research Organization  |
| CSDD    | Center for the Study of Drug Development (Tufts University)                     |
| CTMS    | Clinical Trial Management System  |
| CTP     | Clinical Trial Policy   |

|        |  |
|--------|--|
| CVD    | Cardiovascular disease   |
| D2P    | Direct-to-Participant  |
| DAVP   | Division of Antiviral Products (FDA)                             |
| DM2    | Type 2 diabetes  |
| DOD    | U.S. Department of Defense                                       |
| EDICT  | Eliminating Disparities in Clinical Trials                       |
| ENACTT | Education Network to Advance Cancer Clinical Trials              |
| FDA    | U.S. Food and Drug Administration                                |
| GRACE  | Gender, Race, and Clinical Experience                            |
| H1N1   | <i>Influenza A</i> , subtype H1N1                                |
| HER2   | Human epidermal growth factor receptor 2                         |
| HHS    | U.S. Department of Health and Human Services                     |
| HIV    | Human Immunodeficiency Virus                                     |
| HL7    | Health Level 7   |
| ICC    | Innovative Clinical Concepts, LLC                                |
| ICF    | Informed consent form  |
| ICPS   | Interamerican College of Physicians and Surgeons                 |
| IDE    | Investigational Device Exemption                                 |
| IHS    | Indian Health Service  |
| IMPACT | Increase Minority Participation and Awareness of Clinical Trials |
| IND    | Investigational New Drug Application                             |
| IRB    | Institutional Review Board                                       |
| J&J    | Johnson and Johnson, Inc.  |
| KOL    | Key Opinion Leaders  |
| LEP    | Limited English Proficiency                                      |
| MAUDE  | Manufacturer and User Facility Device Experience                 |
| MRSA   | Methicillin-resistant <i>Staphylococcus aureus</i>               |
| NA     | Native American  |
| NCI    | National Cancer Institute  |
| NCMHD  | National Center for Minority Health and Health Disparities       |
| NCTN   | National Clinical Trial Network                                  |
| NDA    | New Drug Application   |
| NHLBI  | National Heart, Lung and Blood Institute                         |

## ABBREVIATIONS

|       |   |
|-------|---|
| NHMA  | National Hispanic Medical Association                   |
| NHRN  | National Hispanic Research Network                      |
| NIH   | National Institutes of Health                           |
| NMA   | National Medical Association                            |
| NMAC  | National Minority AIDS Council                          |
| NME   | New Molecular Entity                                    |
| NMQF  | National Minority Quality Forum                         |
| NPFR  | National Physician Family Referral Project              |
| NSCLC | Non-small cell lung cancer                              |
| OMH   | Office of Minority Health                               |
| OWH   | Office of Women's Health                                |
| PAD   | Peripheral arterial disease                             |
| PARP  | Poly (ADP ribose) polymerase                            |
| PhRMA | Pharmaceutical Researchers and Manufacturers of America |
| PI    | Principal Investigator                                  |
| QTc   | QT interval corrected for heart rate                    |

|       |  |
|-------|--|
| R&D   | Research and Development   |
| REMS  | Risk Evaluation and Mitigation Strategies                            |
| SANDS | Stop Atherosclerosis in Native Diabetics study                       |
| SMA   | Strategic Medical Associates   |
| SMB   | Safety Monitoring Board  |
| SME   | Subject Matter Expert  |
| SWHR  | Society for Women's Health Research                                  |
| TdP   | Torsades de pointes  |
| TODAY | Treatment Options for Type 2 Diabetes in Adolescents and Youth study |
| TRIPP | Translating Research Into Practice and Policy                        |
| VA    | U.S. Department of Veterans Affairs                                  |
| WHI   | Women's Health Initiative  |
| WISE  | Women's Ischemia Syndrome Evaluation                                 |
| ZCAP  | Zip Code Analysis Project  |

## INTRODUCTION

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Women and ethnic/racial minorities routinely and disproportionately have been excluded from medical product research throughout history. The disparate representation of women and minorities is worrying, as a wealth of scientific evidence shows differing responses to biologics and devices between genders and among racial and ethnic groups.<sup>1</sup> Thus without adequate clinical trial research across diverse populations, the safety and efficacy of a drug or medical device cannot be fully ensured.

Over 18,205 clinical trials are currently seeking volunteers in the United States alone,<sup>\*</sup> providing abundant opportunities for women and minorities to join in the testing of novel disease treatments. Unfortunately, women and minorities are underserved in their ability to access quality medical care. The repercussions of this inequality mean that they are less likely to know about or enroll in clinical trials.

The Society for Women's Health Research (SWHR), a national non-profit organization based in Washington, D.C., was founded in 1990. SWHR is widely recognized as the thought leader in research on sex differences and is dedicated to improving women's health through advocacy, education, and research.

SWHR's signature piece of legislation, the Women's Health Office Act, prompted the establishment of offices of women's health within the Department of Health and Human Services (HHS), including the U.S. Food and Drug Administration (FDA) Office of Women's Health (OWH).<sup>2</sup> The FDA Office of Minority Health (OMH) was established in 2010 to provide leadership and direction in identifying agency actions that can help reduce health disparities to achieve the highest standard of health for all.<sup>3</sup>

Women were first identified as being underrepresented in clinical trials in 1992.<sup>4</sup> Two decades later, this disparity remains, as does the underrepresentation of racial and ethnic minorities. However, the National Institutes of Health (NIH) and FDA, to some extent, over the years have changed their policies to better include females and

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-Garth Graham, Deputy  
Assistant Secretary for  
Minority Health, OMH, FDA

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<sup>\*</sup> According to a search of [www.ClinicalTrials.gov](http://www.ClinicalTrials.gov), the U.S. National Institutes of Health registry and results database of federally and privately supported clinical trials; correct as of 2011 Oct 4.

minorities in medical research. The NIH Policy on Inclusion of Women & Minorities in Clinical Research was mandated by Congress in 1993.<sup>5</sup> It stipulates that:

- ◆ Women and minorities must be included in all clinical research studies.
- ◆ Women and minorities must be included in Phase III clinical trials in numbers adequate for valid analysis.
- ◆ Cost is not allowed as an acceptable reason for exclusion.
- ◆ NIH must support outreach efforts to recruit and retain women, minorities, and their subpopulations in clinical studies.

However, this law applies only to NIH-funded research. In 2005, FDA outlined its own “non-binding” recommendations to industry for a standardized approach to the collection of race and ethnicity data.<sup>6</sup> Clinical findings must now be reported by sex, race and age, but there are currently no laws or official policies which require inclusion of women and/or minorities in industry-sponsored clinical trials.

In response to a demand for better strategies in recruiting women and minorities to clinical trials, SWHR and FDA’s OWH, with the support of FDA’s OMH, hosted “Dialogues on Diversifying Clinical Trials: Successful Strategies for Engaging Women and Minorities.”<sup>\*</sup> The agenda was specifically structured to inspire participants to share successful experiences in clinical trial recruitment and to encourage collaboration across disciplines. Participants were challenged to:

1. Identify novel means to increase the participation of underrepresented and underserved populations in clinical trial research, and
2. Share successful and innovative practices in recruitment, retention and analysis of women and minorities in clinical trials research.

In her introduction at the “Dialogues on Diversifying Clinical Trials” meeting, Phyllis Greenberger, MSW, President and CEO of SWHR, stated that much progress must be made before reaching equality in medical research and treatment. She asked, “How do we know that research that’s primarily done on young, White, healthy males can be extrapolated to women?” This “one-size-fits-all” approach does not apply with respect to age, gender, race or ethnicity. These factors are becoming increasingly important as we enter an era of personalized medicine.

Jose Reynal, MD, member of the Diversity Committee of the Pharmaceutical Research and Manufacturers of America (PhRMA), provided the industry perspective: “The pharmaceutical industry cares about making sure we have an adequate number of women and minorities recruited in our clinical trials.” One particular goal for the pharmaceutical industry is to identify new ways to streamline the recruitment process. Furthermore, the industry predicts that regulatory agencies will mandate that trials include proportional representation of those most likely to be served by the drug. For

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President and CEO of the  
Society for Women’s Health  
Research

<sup>\*</sup> September 22-23, 2011, Washington, D.C. All presentations referenced in this report can be found online at: [http://www.womenshealthresearch.org/site/PageServer?pagename=events\\_clinicaltrials](http://www.womenshealthresearch.org/site/PageServer?pagename=events_clinicaltrials).

instance, a trial for sickle cell anemia treatment should include a larger number of people from African and Mediterranean descent, as the disease is more commonly found within those groups.

Garth Graham, MD, MPH, FACP, Deputy Assistant Secretary in the HHS Office of Minority Health, described the current climate in the healthcare debate as a “revolutionary time.” In his introduction, he said that, “There are changes happening in healthcare like we have never had before.” Marsha Henderson, MCRP, Assistant Commissioner for Women’s Health at FDA, conceived the idea for the meeting and described it as an “extraordinary day” that was “long overdue.”

Margaret Hamburg, MD, FDA Commissioner, concluded the introduction, emphasizing that the participation of women and minorities is central to the well-being of all Americans, and that the goals for improving healthcare cannot be reached until both groups are adequately represented. She added that participation rates for women and minorities have improved over the last several decades; enrollment for women averages 50% in late-phase trials,<sup>7</sup> but remains between 21-32% in early stages of research.<sup>8</sup> These numbers, according to Hamburg, are “not nearly adequate,” and the same can be said for racial and ethnic minorities. “Dialogues on Diversifying Clinical Trials” was presented as an opportunity to strengthen ongoing collaborations and build new partnerships. Dr. Hamburg stressed that it represents a great step to build on, and that a common ground must be reached to continue momentum and to develop new approaches to recruit and retain women and minorities in medical research.

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<sup>1</sup> Institute of Medicine (U.S.) Committee on Understanding the Biology of Sex and Gender Differences. “Exploring the Biological Contributions to Human Health: Does Sex Matter?” Washington, D.C.: National Academy Press; 2001. Available from: [Accessed:

<sup>2</sup> Women's Health Office Act of 1994, H.R. 3874, Sec. 6., 103d Cong., 2d Sess. (1994); included in the Patient Protection and Affordable Care Act of 2010. P.L. 111-148. (2010).

<sup>3</sup> Patient Protection and Affordable Care Act of 2010. Pub. L. no. 111-148, 124 Stat 119 (2010).

<sup>4</sup> U.S. Government Accountability Office. “Women's Health: FDA Needs to Ensure More Study of Gender Differences in Prescription Drug Testing”. (GAO/HRD-93-17). Washington, D.C.: 1992.

<sup>5</sup> National Institutes of Health Revitalization Act of 1993. Pub. L. no. 103-43, 107 Stat 122 (1993).

<sup>6</sup> U.S. Food and Drug Administration [Internet]. “Guidance for Industry: Collection of Race and Ethnicity Data in Clinical Trials.” Rockville, MD: U.S. Department of Health and Human Services; Copyright 2005. Available from: <http://www.fda.gov/RegulatoryInformation/Guidances/ucm126340.htm>. [Updated: 2010 Jul 30; Accessed: 2011 Oct 26].

<sup>7</sup> Poon R., et al. Participation of Women and Sex Analyses in Late Phase Clinical Trials of New Molecular Entity (NME) Drugs and Biologics Approved by the FDA in 2007-2009. *Drug Information Association*. 2011 Jun.

<sup>8</sup> Pinnow E., et al. Increasing participation of women in early phase clinical trials approved by the FDA. *Women's Health Issues*. 2009; **19**:89-93.



## WOMEN AND MINORITIES IN CLINICAL TRIAL RESEARCH: A HISTORICAL PERSPECTIVE

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### ADDRESSING RACIAL AND ETHNIC HEALTH DISPARITIES WITHIN THE STATE OF MARYLAND: THE UNIVERSITY OF MARYLAND CENTER FOR HEALTH EQUITY

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#### THE UNIVERSITY OF MARYLAND CENTER FOR HEALTH EQUITY

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Stephen Thomas, PhD, is Director of the University of Maryland, Center for Health Equity (CHE). CHE has been designated with the challenging task of addressing racial and ethnic health disparities within the state of Maryland. The difference in quality of healthcare for majority versus minority populations goes beyond simply incidence and prevalence of disease. Racial disparity stems from the broken healthcare system itself, along with discrimination, bias and stereotype of healthcare professionals.<sup>9</sup>

An examination of AIDS cases by race and ethnicity reveals an alarming trend in increased diagnoses in the Black and Hispanic populations over the last three decades. Between 1985 and 2008, the percentage of AIDS cases increased in African-Americans by 30%, while in the White population, this percentage decreased by the same amount over the same period.<sup>10</sup> This information is essential in identifying the groups most in need of intervention in specific areas of healthcare. The current movement to eliminate racial and ethnic identifiers should thus be reconsidered, as the data may be crucial to reducing disparities in healthcare.

Between 1985 and 2008, the percentage of AIDS cases increased in African-Americans by 30%.<sup>10</sup>

#### MINORITY DISTRUST OF MEDICAL RESEARCH

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When considering the importance of race, Dr. Thomas pointed out that a legacy of scientific racism that has left a cultural memory in minority populations “may shape how they respond to our efforts to recruit them to research.” These attitudes and behaviors are influenced by books and movies in popular culture, which give minorities legitimate reasons to distrust the scientific establishment. Thus, industry, academics, and advocacy groups must examine and be sensitive to these highly prejudicial sources and their effect on cultural attitudes.

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The National Bioethics Research Initiative “Building Trust between Minorities and Researchers”<sup>11</sup> aims to assess the knowledge, attitudes and behaviors of African-Americans and Hispanics toward participation in research. The randomized national study consisted of a telephone survey of 2,455 participants. The findings revealed that many minorities believe in the importance of health and scientific research. However, despite a willingness to participate, many have never been asked. While there are apprehensions toward certain procedures, 65-80% of African-Americans and Latinos would be willing to provide essential biological samples such as blood and DNA.<sup>12</sup> The top reasons they identified for participation related to helping others, themselves, or relatives with the disease. Also encouraging was that the majority of Latinos and African-Americans believed that researchers were honest about the risks of participation.

#### MINORITY RECRUITMENT IN CLINICAL TRIALS

The NIH-supported Healthy Black Family Project is a community-based demonstration project designed for health promotion and disease prevention.<sup>13</sup> The 7,000 participants in the study were encouraged to increase physical activity, improve nutrition, and reduce stress. The project also questioned participants on their family history of disease and followed-up with information on clinical trials most applicable to their own health issues. More than half of these individuals had a moderate or high risk of hypertension (71%), diabetes (58%), or cardiovascular disease (55%) based on their genetic family health history.<sup>14</sup> Dr. Thomas stated the importance of raising the issue in “normal settings where people live, work, and play.” Health Advocates in Reach (HAIR) is a community-based intervention that utilizes barbers and stylists to deliver health messages to the Black community in barbershops and beauty salons. People are more receptive to seeing the average person than a celebrity. The television public awareness campaign for Building Trust promotes a longer, healthier life, thanks to medical research.

Changing minority public perception of research is not the end of the line in promoting clinical research participation. Dr. Thomas pointed out that the gay community sent a powerful message by demanding to be involved in AIDS research, and that similar grassroots movements could be beneficial for other minority groups. Such efforts would prompt response from government and industry to result in better inclusion of minorities in trials and better healthcare for all. Healthcare professionals and researchers can no longer make excuses for a lack of minority participation.

<sup>9</sup> Balsa A. I. and McGuire T. G. Prejudice, clinical uncertainty and stereotyping as sources of health disparities. *J Health Econ.* 2003; **22**(1):89-116.

<sup>10</sup> Centers for Disease Control and Prevention. "AIDS Trends." [Updated: 2010 Jul 22; Accessed: 2012 Jan 11]. Available from: <http://www.cdc.gov/hiv/topics/surveillance/resources/slides/trends/slides/trends.pdf>.

<sup>11</sup> Funded by the National Institutes of Health American Recovery and Reinvestment Act 7RC2MD004766; Principal Investigator, S.B. Thomas.

<sup>12</sup> Data presented by S. Thomas in "Dialogues on Diversifying Clinical Trials," Washington, D.C., 2011 Sept 22. [http://www.womenshealthresearch.org/site/PageServer?pagename=events\\_clinicaltrials](http://www.womenshealthresearch.org/site/PageServer?pagename=events_clinicaltrials).

<sup>13</sup> Thomas S. B. and Quinn S. C. Poverty and Elimination of Urban Health Disparities. *Ann NY Acad Sci.* 2008; **1136**(1):111-25.

<sup>14</sup> *Ibid.*

KEN GETZ, MBA, is a Senior Research Fellow and Assistant Professor at the Tufts Center for the Study of Drug Development at Tufts University, Founder of the Center for Information & Study on Clinical Research Participation (CISCRP).

## CISCRP: HISTORICAL OVERVIEW: WOMEN AND MINORITIES IN CLINICAL TRIAL RESEARCH

### BACKGROUND: CISCRP

The Center for Information & Study on Clinical Research Participation (CISCRP) is a non-profit organization that promotes education and awareness of the clinical research enterprise. Ken Getz, MBA, provided a historical context into the complexity of the issues surrounding women and minority involvement in clinical trial research. Firstly, diversification in clinical trials matters to industry for four main reasons:

- ◆ Greater diversity opens a window to recruiting more patients into clinical trials.
- ◆ Changes in demographics over the next ten years mean that minority populations may be the majority in the future, a feature that makes diversification financially attractive.
- ◆ Because incidence of disease and response to treatment varies between genders and among racial and ethnic groups, safety and efficacy should be evaluated in stratified populations.
- ◆ Industry must improve its image by responding to public and policymaker concerns.

Half of all clinical trials are conducted outside America.\* By moving outside the U.S., companies feel they are reaching populations that are more diverse. Furthermore, the use of smaller trial sites in greater numbers allows companies to hedge investigative site performance and reduces loss when one center fails. Since 1997, the average number of Principal Investigators (PIs) per study has more than doubled, while the mean number of patients per site has decreased by over 50%.<sup>15</sup>

### ENGAGING MINORITY PATIENTS AND PHYSICIANS

Getz asserts that with regard to the type of diseases targeted in clinical trials, industry does believe it is addressing diverse populations. Over the last two decades, there has been a dramatic increase in the number of medicines being developed which disproportionately affect women, Hispanics, and African Americans.

The percentage of racial and ethnic minorities in clinical research is particularly disparate in industry-funded clinical trials. Whites account for 66.9% of the total U.S.

\* Refers only to studies registered with ClinicalTrials.gov; Global total: 119,213; U.S. studies: 58,874; data correct as of 13 Jan 2012.

population, but make up 83.3% of trial participants.<sup>16</sup> Minority enrollment in NIH-funded clinical research is in close proportion to the population, but less so with regard to gender, where women make up a majority 63.1% of study volunteers.<sup>17</sup>

Like Dr. Thomas, Getz also highlighted the high willingness of minority patients to participate in clinical research. Empirical data shows that minorities, particularly African-Americans and Hispanics, are as willing, and in some cases, more willing than Whites are to participate in health research.<sup>18</sup> The primary drivers of low minority representation are poor “clinical research literacy” and access to centers involved in clinical trials. The difference in distrust of physicians or PIs is less of a factor today than in previous decades, but lack of trust lies in the entire public, not just minorities.

It is also important to examine the representation of physicians in clinical trial investigation, as the physician’s race and gender may influence the race and gender of study volunteers. Interest in clinical research participation is similar among physicians, regardless of sex or ethnicity; however, women and minority doctors are less represented in conducting clinical trials. This is particularly significant in industry, and women and minority physicians on average are involved in fewer studies annually and throughout their career.

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To women physicians, clinical trial investigation is less prestigious and economically unattractive. The number of female investigators in the U.S. has declined from 15.1% in 1990 to 10.9% in 2006.<sup>19</sup> Minority investigators, on the other hand, feel it is hard to routinely find clinical trials in which they can participate. Women and minority physicians both cite the difficulty of finding and retaining volunteers and the slow grant payment process as reasons for not participating in trials. Getz presented anecdotal evidence that suggests that women and minority physicians realize how burdensome clinical trials are and do not want to return.

#### INDUSTRY NEEDS INCENTIVES

From the industry perspective, it is difficult to find and attract experienced minority and female PIs. If industry does want to increase investigator diversity, industry should be responsible for providing the infrastructure and community support to recruit and retain participants. However, women and minority PIs are relatively more costly to engage. This factor is crucial when there is high pressure to increase return on investment in the drug development process. As a result, there is little incentive for industry to change the status quo, especially considering that when they are already recruiting minority and female patients, the need for minority and female investigators seems less important. Getz says that it is “market attractiveness and business decisions that will ultimately provide success to the organizations that sponsor research, as well

as to the patients who will benefit from these therapies.”

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<sup>15</sup> Data presented by K. Getz in "Dialogues on Diversifying Clinical Trials," Washington, D.C., 2011 Sept 22.

[http://www.womenshealthresearch.org/site/PageServer?pagename=events\\_clinicaltrials](http://www.womenshealthresearch.org/site/PageServer?pagename=events_clinicaltrials).

<sup>16</sup> U.S. Census Bureau; National Institutes of Health; Tufts CSDD, 2010.

<sup>17</sup> *Ibid.*

<sup>18</sup> Wendler D., et al. Are Racial and Ethnic Minorities Less Willing to Participate in Health Research? *PLoS Med.* 2006 Feb; **3**(2):e19.

<sup>19</sup> Tufts Center for the Study of Drug Development (CSDD), 2007.

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## PROVIDER/INVESTIGATOR PERSPECTIVES ON CULTURAL AND LINGUISTIC COMPETENCY IN CLINICAL TRIALS RESEARCH

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E. FRANCIS  
JONES is  
Founder,  
President, and  
CEO of Innovative  
Clinical Concepts,  
LLC

### AFRICAN-AMERICAN CULTURAL PERSPECTIVE: EFFECTIVE COMMUNICATION STRATEGIES

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Innovative Clinical Concepts, LLC (ICC) is a clinical trial research service organization that provides specialized services to study sponsors and clinical research organizations (CROs), with a focus on physicians and clinical practices who serve minority, underrepresented, and women patient populations. ICC works to bring minority physicians into clinical trials. E. Francis Jones discussed three requirements for effective communication with African-American physicians:

- ◆ Development of effective strategies for communication
- ◆ Implementation of a coherent plan of action
- ◆ Identification of major factors such as goals and objectives, operational constraints and imperatives, and pertinent conditions in the environment

### CONSIDERATIONS FOR COMMUNITY-BASED AFRICAN-AMERICAN PHYSICIANS

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The majority of African-American physicians are community-based,<sup>20</sup> and while they are interested in conducting clinical trial research, their work environment is different from physicians based in academic, hospital, or institutional settings. First, most still have paper medical records and often experience high staff turnover. They may also have a large patient population, with the physician seeing over thirty patients a day. Some of these patients may qualify to enroll in a study, but the busy environment and lack of

infrastructure to support the trial prevents this. The routine activity of a typical doctor's office is demanding, and in itself becomes an obstacle.

Community-based physicians must also consider their bottom-line. Jones gave an example of a questionnaire provided to minority investigators, for which the sponsor received no responses. The thirteen-page form indicated it would require twenty minutes to fill out, time that the community-based minority investigator could devote to seeing patients, and thus would lose money by filling it out. Without knowledge of clinical trials, the necessary infrastructure, and incentive for participation, physicians will not view it as a valuable use of their time.

### COMMUNICATING EFFECTIVELY WITH PHYSICIANS

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In the original questionnaire, the physicians reacted to what they saw – a lengthy document with a great deal of information – in reality, there were not that many questions. Had the sponsor communicated more effectively, the physicians may have realized this. Jones went on to identify the key areas where information was needed from the physicians. By including only the most relevant information, she reduced the questionnaire time to five minutes and received a high rate of response. Due to the follow-up, many of the minority physicians were considered for the trial. The lesson learned from this experience was that the sponsor must carefully construct the information provided to the physicians and its presentation. They must consider the physician when writing trial protocols and feasibility questionnaires. This applies to all doctors, not just minorities.

In Jones' experience, African-American physicians are focused on their own practice, and are not well-informed about the clinical trial process. Trial sponsors must inform doctors that they will benefit from participating in trials, not just for their businesses, but their patients as well. Furthermore, sponsors must guarantee the physician that he or she will be justly considered for the study.

In summary, minority patients are available and willing to participate in clinical trials, and minority doctors typically have greater numbers of minority patients. Therefore, the doctors must be involved because they are responsible for providing access to the patients. Jones also noted that novice investigators can be the best performers, and industry must be committed to engaging these physicians in clinical trials.

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<sup>20</sup> Data presented by E.F. Jones in "Dialogues on Diversifying Clinical Trials," Washington, D.C., 2011 Sept 22.  
[http://www.womenshealthresearch.org/site/PageServer?pagename=events\\_clinicaltrials](http://www.womenshealthresearch.org/site/PageServer?pagename=events_clinicaltrials).

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## MAKING CLINICAL TRIAL DIVERSITY A REALITY

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### THREE CULTURES IN DISHARMONY

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James Powell, MD, CPI, leads Project IMPACT (Increase Minority Participation and Awareness of Clinical Trials), an initiative of the National Medical Association (NMA) aimed at increasing the awareness, knowledge, and participation of African-American physicians and consumers/patients in all aspects of biomedical research and clinical trials.

In identifying the barriers that prevent minority participation in clinical trials, Dr. Powell described three cultures in disharmony. First, the pharmaceutical industry has a tendency to repeatedly use investigators, and those novice PIs brought into studies are more often carrying out studies outside the U.S. Of his own experience in the industry, Dr. Powell observed that there was “never enough time to do it right, but always enough time to do it over.” The second culture was that of the physicians, who are uneducated about trials, are not interested in participating and lack the infrastructure to do so, and are concerned about their own investment. Of the patient culture, Dr. Powell noted that while it is recognized that patients do not trust the industry, physicians typically share the same mistrust of the commercial medical research industry. The rifts between these three groups, such as ethical and regulatory barriers, knowledge void, and lack of trust, must all be overcome to successfully and efficiently bring minority groups into clinical trials.

### EDUCATION AND TRAINING

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Project IMPACT strives to overcome these barriers and encourage minority enrollment. The primary means to achieving this goal is through education. Consumers must be aware of the clinical trial process, its history and its abuses, but also need to know that society, and they as individuals can benefit from trial participation. Most importantly, they need to be made aware of the ways in which they can get involved. Mistrust of the industry is often used to explain ineffective recruiting strategies. Although it does exist, mistrust is not a valid excuse, as minorities have already shown their willingness to volunteer for trials.

The other, and equally important half of education, pertains to physician awareness and training. Part of the work of Project IMPACT is to train physicians to be investigators. The industry must educate physicians, even those who are not investigators, but at the same time, physicians must be responsible and educate themselves *and* their patients. Speaking of the doctors he worked with through Project IMPACT, Dr. Powell said, “one hundred percent of [physician investigators] said that their involvement in clinical trials led to an improvement in care for their patients.”

In addition to the traditional education for investigators on trial ethics and regulation, Project IMPACT also provides training on the business aspect of successful clinical trials, and “cultural competence.” Project IMPACT advocates diversity at every level of the

trials process, and works on ways to improve trial design to achieve “meaningful answers from the diverse communities in clinical trials.”

Despite training, minority physicians often are not given the opportunity to be trial investigators. Much of this is due to the tendency of the industry to reuse investigators. Rather than asking patients to trust qualified physicians, industry must invest in qualifying trusted physicians. There is evidence that minority patients more often seek care from physicians of their own race.<sup>21</sup> As a result, by utilizing minority investigators, they are much more likely to enroll minority patients in the trial.

#### A COMMUNITY-DRIVEN APPROACH TO TRIAL RECRUITMENT

It is clear that conventional methods for clinical trial recruitment do not promote ethnic balance. Project IMPACT made a proposal to industry in 2009 to make changes to the current system, but due to a number of factors and changes in leadership, the proposal was never implemented. Rather than wait for industry to change from within, Dr. Powell’s company, Strategic Medical Associates, LLC (SMA), “flipped the model” for what was traditionally an industry-driven enterprise to a community-based one ( Figure 1, page 14).

This approach allows communities to be actively involved in research, and SMA showed that this innovation was effective in increasing patient diversity. However, in the absence of a regulatory mandate, there is little incentive for sponsors to change from the status quo. Furthermore, both sponsors and physicians are concerned with their own profits, thus any sustainable effort to achieve ethnic balance must do so without compromising speed and cost. The ACTION Plan (Alliance for Clinical Trial Trustworthiness In Our Neighborhoods) is an innovative and comprehensive, community-driven program for achieving superior speed, efficiency, and ethnic balance in clinical trials.

Minority patients more often seek care from physicians of their own race.<sup>21</sup>



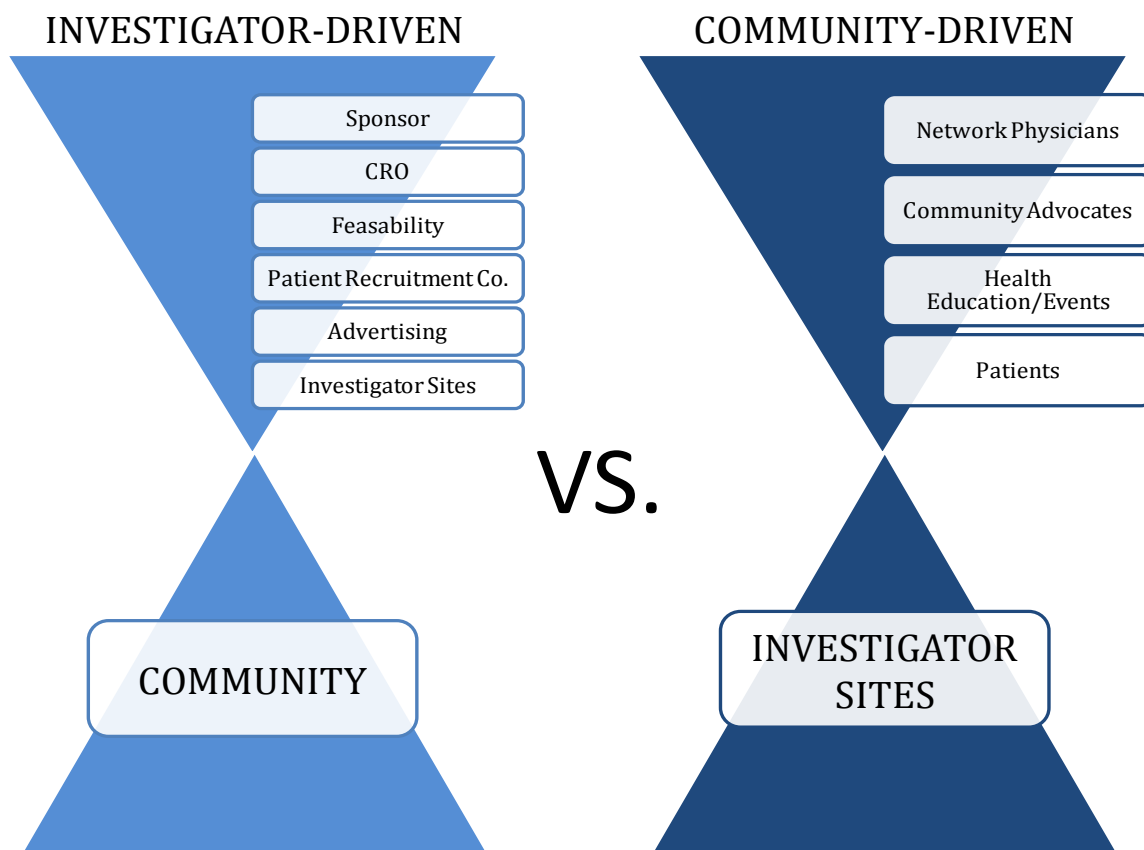


Figure 1. Traditional investigator-driven model for clinical trial patient recruitment vs. an innovative community-driven approach. Adapted with permission © 2011 Strategic Medical Associates, LLC.

<sup>21</sup> Saha S., et al. Do patients choose physicians of their own race? *Health Affairs*. 2000; **19**(4):76-83.

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## NATIVE AMERICAN PERSPECTIVES IN CULTURAL AND LINGUISTIC COMPETENCY IN CLINICAL TRIALS

### DISTRUST OF MEDICAL RESEARCH AMONG NATIVE AMERICANS

Native Americans exhibit higher medical mistrust and lower satisfaction with healthcare delivery systems in the U.S.<sup>22</sup> This distrust stems from a tragic history of medical abuse. During the 1960s and 1970s, medical procedures, including sterilization (by hysterectomy or tubal ligation), were performed on Native American women without informed consent.<sup>23</sup> More recently, DNA samples from an Arizona-based study on diabetes in the Havasupai tribe were used for other research purposes without permission, for which the tribe received a settlement from Arizona State University.<sup>24</sup> These and numerous other accounts have made Native Americans naturally suspicious

of researchers. Dr. Lillian Tom-Orme is a member of the Diné or Navajo Nation, and admits that she herself is often suspect of investigators entering the community.

To further compound this mistrust, the communities that have participated in medical research were not informed of the outcomes. This has led many Native Americans to believe that research does not result in improved health, and that studies are beneficial only to the researchers.

### BUILDING TRUST WITH NATIVE AMERICAN COMMUNITIES

Based on the attitude of Native Americans to medical research, a huge part of recruiting patients from these communities is gaining their trust. Native Americans seek considerable background information before agreeing to participate. They want to know about the investigators and their institutional backgrounds, and may ask questions such as, “Does your institution have experience working with us?” They also want to know the purpose and of the research and its novelty compared to previous studies. Potential benefits to the community are also important, and researchers must explain that there may not be immediate and/or direct benefits.

Dr. Tom-Orme has worked on clinical trials with American Indian and Native Alaskan populations. Of the Native American culture, she said, “things happen very slowly. We don’t usually like to see researchers come in and go the next day.” These communities appreciate a researcher who is willing to take the time to invest in them as people, not just as subjects in a medical study. In her own research, she spent two to three years sitting down with Native American and Native Alaskan community members. Trial sponsors must recognize that recruiting patients from these communities does not occur rapidly; it can take a long time to inform the study members and earn their involvement.

When Dr. Tom-Orme followed-up with patients after a large diabetes trial, the response was positive. Study participants said they learned a great deal, despite the fact that no educational intervention was implemented. The time and effort spent recruiting these patients at the beginning of the study paid off, for both the researchers and the participants. This underscores the need for transparency and communication with the Native American population, and understanding of the cultural norms of the community.

### UNDERSTANDING CULTURAL DIFFERENCES

Native American and Native Alaskan peoples often have strong opinions about what type of research methods are appropriate, based on their spiritual or cultural beliefs. These beliefs may differ from those of the sponsor or principal investigators. For example, the lead researcher in the Arizona State University study of the Havasupai tribe maintains she was “doing good science,” but failed to consider or understand the need for consent from the Havasupai, for whom blood has deep spiritual meaning. Dr. Tom-Orme hoped to make her own diabetes study longitudinal, but the Native American community was unhappy when the research moved toward genetics.<sup>25</sup> Thus,

cultural sensitivity is vital when considering the type of research or samples being collected.

Advocates of community-based participatory research (CBPR) emphasize the need for collaborative efforts, to ensure that both parties fully understand ethical and regulatory guidelines. Current frameworks that address the rights of property, ownership, and privacy as they pertain to medical research, may not fully address the concerns of Native peoples, and should be reviewed in a separate context.<sup>26</sup> As there are few IRBs among Native American communities, sponsors are encouraged to enlist a Native American representative, something which Native American college students said would increase their willingness to participate.<sup>27</sup> The same was true of elder American Indians and Alaska Natives (AIANs), who also emphasize desire for a study doctor with experience treating their race/tribe/community, along with family support.<sup>28</sup> Other positive aspects to encouraging participation are the bringing of resources to the community or new treatments or services; concerns over discrimination and confidentiality are negative influences.<sup>29,30</sup>

From her experience in working with AIAN communities, Dr. Tom-Orme recommends that researchers avoid “yes-no” questions in favor of “who, what, how, where, and when” but not “why.” She encourages investigators to: clearly explain all technical terms, verbally and written; communicate interactively, using slides, photos, drawings; and learn native words, such as “hello” or “thank you” to show genuine interest. The role of women is also highly important in AIAN communities and as such, it should not be overlooked.

#### AIAN POPULATIONS PROVIDE IMPORTANT CLINICAL TRIAL INFORMATION

Dr. Tom-Orme has tried to push not only for inclusion of Native Americans in studies, but also stratification of results, so that these communities can learn the results specific to themselves. She was told by leaders of the National Children’s Study that there was no difference between the large population of Hispanics and the very small number of Native American participants. She asserts that inclusion of one minority group does not make up for lack of another; minority groups differ among each other just as they do from White Americans.

In conclusion, when working with AIAN populations, it is essential to develop a trusting partnership at all levels of the community: individual, program, tribal leadership, traditional leaders, healthcare providers, etc. This trust stems from strong

“Researchers must **understand** the **cultural norms** of the community.”

-Lillian Tom-Orme, PhD, Division of Clinical Epidemiology, University of Utah School of Medicine

communication on all aspects of the study and from carefully addressing the specific needs of that community based on good understanding of their cultural background. Researchers should understand the Native Americans' reluctance to participate in research, and emphasize the benefits of the research and inform them of study outcomes.

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<sup>22</sup> Guadagnolo B. A., et al. Medical Mistrust and Less Satisfaction With Health Care Among Native Americans Presenting for Cancer Treatment. *J Health Care Poor Underserved*. 2009; **20**(1):210-26.

<sup>23</sup> Lawrence J. The Indian Health Service and the Sterilization of Native American Women. *American Indian Quarterly*. 2000; **24**(3):400-19.

<sup>24</sup> Harmon A. "Indian Tribe Wins Fight to Limit Research of Its DNA." *The New York Times*, Available from: <http://www.nytimes.com/2010/04/22/us/22dna.html?pagewanted=all>. [Updated: 2010 Apr 22; Accessed: 2011 Nov 2].

<sup>25</sup> *Ibid*.

<sup>26</sup> Tsosie R. Cultural challenges to biotechnology: Native American genetic resources and the concept of cultural harm. *J Law Med Ethics*. 2007 Fall; **35**(3):396-411.

<sup>27</sup> Noe T. D., et al. The influence of community-based participatory research principles on the likelihood of participation in health research in American Indian communities. *Ethn Dis*. 2007 Winter; **17**(1 Suppl 1):S6-14.

<sup>28</sup> LaVallie D. L., et al. Encouraging American Indians, Alaska Natives to participate in cancer clinical trials. *Ethn Dis*. 2008 Spring; **18**(2):236.

<sup>29</sup> Noe T.D., et al. *Op. cit*.

<sup>30</sup> La Vallie D.L., et al. *Op. cit*.

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## THE NATIONAL HISPANIC RESEARCH NETWORK

### ENGAGING HISPANIC PHYSICIANS IN CLINICAL TRIALS

The goals of the Interamerican College of Physicians and Surgeons (ICPS) are to improve the health of the Hispanic community and opportunities for Hispanic physicians, and encourage Hispanics to pursue careers in healthcare. The National Hispanic Research Network (NHRN) provides education and resources to Hispanic physicians at the local level to encourage their participation in clinical studies.

Hispanics make up 16% of the U.S. population but account for only 1% of clinical trial participation.<sup>31</sup> In order to rectify the situation, Hispanic physicians are critically needed to participate as investigators in clinical trials. In response, NHRN was established by ICPS in 2007, and since then has recruited 756 of their goal of 1,000 Hispanic physicians. NHRN members represent all specialties of medicine, but the majority is involved in internal or family medicine, general practice, or pediatrics.

**Hispanics** make up **16%** of the US population but only **1%** of clinical trial research participants.<sup>31</sup>

The program has had a 13% attrition rate over the four years. The majority of these members left because they were dismayed with the lack of support and interest from industry in considering them for trials. Of the 170 novice researchers who applied for investigator roles, less than 5% were approved. The application process for clinical trials is not an easy task, and Hispanic physicians want to be approved. These low acceptance rates lead them to question if applying is worth the effort.

#### NHRN CLINICAL TRIALS

Many of the trials supported by the NHRN team are “easy” trials, in either Phase III or IV. James Tierney, MA, MBA, of ICPS said, “It seems that the industry is a lot more willing to give novice researchers easy trials.” These physicians’ lack of experience makes for an unfortunate “Catch-22” – without experience they cannot be accepted into trials, and without acceptance into trials, they cannot gain experience.

NHRN trials have recruited only 195 patients, the majority of which are Hispanic or Latino (78%), but Asians (16%), Blacks (4%), and Whites (2%) are enrolled as well. Of these, less than 2% had experience participating in at least one trial and less than 1% had a family member who had participated in at least one trial. However, of the eligible patients screened for enrollment, 97% consented to participate, and all surveyed participants overwhelmingly stated that they would recommend their relatives to participate in clinical trials.

#### CONTINUING NHRN WORK

Overall, the NHRN program has been very effective in recruiting Hispanic physicians and minority patients to participate in clinical trials. The primary obstacle is getting experience for these Hispanic physicians, and although NHRN physicians are novice researchers, ICPS has been successful in enrolling members in trials and supporting them as they participate. In 2009, NHRN collaborated with Arysmed, LLC to secure trials for NHRN, however funding from AstraZeneca ran out in December 2010. Tierney listed several other trial sponsors and CROs that have shown interest in utilizing novice Hispanic researchers from NHRN, but financial support and additional clinical trials are needed.

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<sup>31</sup> Data presented by J. Tierney in "Dialogues on Diversifying Clinical Trials," Washington, D.C., 2011 Sept 22.  
[http://www.womenshealthresearch.org/site/PageServer?pagename=events\\_clinicaltrials](http://www.womenshealthresearch.org/site/PageServer?pagename=events_clinicaltrials).

## THE VITAL ROLE OF COMMUNITIES IN CLINICAL TRIALS

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### “TAKING IT TO THE STREETS”: MINORITY RECRUITMENT THROUGH COMMUNITY ADVOCACY

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Patricia Sanders, APR, discussed two of the most relevant of her “Ten Commandments for Recruiting African-Americans into Clinical Trials.” These “commandments” came directly from the communities of minorities most in need of outreach efforts for clinical trial awareness and recruitment. Sanders explained that few of the industry and government leaders who address the problem of minority representation in clinical trials actually take action.

*IV: Takin’ It to the Streets: Thou shalt evaluate community involvement of the site investigators – as a tool to outreach more African-Americans.*

“Takin’ It to the Streets,” refers to outreach efforts enforced within the Black community. A drug trial sponsored by Actelion Pharmaceuticals required that subjects have both sickle-cell anemia and hypertension,<sup>32</sup> and they requested support from P&E to find the patients who met the criteria for eligibility. P&E first sent letters of appreciation to community organizations asking for support, and created a calendar of events to increase awareness, including Health Expos, barbeques, church-sponsored events, and other events taking place within the African-American community. They contacted community organizations to tie information about the trial into their summer picnics and activities. Investigator sites were surveyed to find physicians, nurses, and staff who were active in their communities and would be willing to take IRB-approved materials to community gatherings. P&E invited physicians to a luncheon where they presented medical updates on sickle-cell anemia and explained why this trial was especially necessary. From the thirty doctors they hosted from surrounding hospitals, twenty signed up to participate, and within sixty days, Actelion had enrolled five African-American patients.

*IX: Ride the Soul Train: Thou shalt build a house of trials around community networks and involvement in ongoing clinical trial education – as a tool for TRUST in the community.*

Sanders advised sponsors and trial sites that they “...cannot expect to recruit minorities in minority communities if they never see or hear from you except when you want something from [them].” She advocated for community organizations that bring attention to health issues and clinical trials on a regular basis and gain trust from the community. When trials become available, a reputable network to recruit patients is already in place, as is the infrastructure to recruit and carry out the trials.

"[Patients] must know that they have **choices**, that they are in **control** of their **destiny** of this disease."

-Patricia Sanders, Senior Consultant, P&E Associates

#### THE CEDRICT STUDY

CEDRICT (Coalition to Eliminate Disparities and to Research Inclusion in Clinical Trials) is a field research study launched in 2009 by the National Physician Family Referral (NPFR) Project to gather information about the health education needs and access to clinical trials by African-Americans from *their* point of view.<sup>33</sup> It measured attitudes about access to current health information, and their willingness to participate in clinical trials under various conditions.

Sponsors recruiting minority patients often encounter a gap in disease education, but they take the stance that education is not their responsibility. That said, African-Americans surveyed in the CEDRICT study indicated that disease education was of great importance to them. Sponsors must take heed of this fact, and realize that it is difficult to discuss enrollment in a clinical trial if the patient is not aware of all of his or her treatment options, or worse, knows little about the disease itself. According to Sanders, "[Patients] must know that they have choices and that they are in control of their destiny of this disease." They must also have "enough information to make intelligent choices about participating in clinical trials."

A larger problem, she says, is how to effectively network in African-American communities, and build trust through providing ongoing clinical trials. In Detroit, Michigan, and Dallas/Ft. Worth, Texas, community clinical trials coalitions made up of medical professionals and lay people are successfully providing ongoing education and access to trials. The CEDRICT program has grown to include an AACT (African-Americans in Clinical Trials) Coalition Component designed to collaborate with these existing clinical trials education groups to specifically engage the African-American community and health advocates and networks that focus upon racial disparities in healthcare and clinical trials.

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<sup>32</sup> *Actelion Smadar Trial Registry* [Internet]. "Trial Registry ASSET-1." Switzerland: Actelion Pharmaceuticals Ltd.; Copyright 2005. Available from: [http://trials.actelion.com/asp/Trial\\_Registry/StudyInfo.asp?ST=AC-052-368](http://trials.actelion.com/asp/Trial_Registry/StudyInfo.asp?ST=AC-052-368). [Updated: 2007 Jul 28; Accessed: 2011 Nov 2].

<sup>33</sup> *National Physician and Family Referral Project* [Internet]. "C.E.D.R.I.C.T." Dallas, TX: National Physician and Family Referral Project; Copyright 2010. Available from: [http://www.npfrproject.org/\\_newsite/cederictovr.php#FRComponent](http://www.npfrproject.org/_newsite/cederictovr.php#FRComponent). [Updated: 2010; Accessed: 2012 Jan 12].

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## PROMOTING RECRUITMENT AND RETENTIONS OF AFRICAN-AMERICAN WOMEN IN FAITH-BASED HEALTHY LIFESTYLE PROGRAMS: SISTER TALK HARTFORD

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### THE SISTER TALK HEALTHY LIFESTYLE PROGRAM

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Judith Fifield, PhD, was Principal Investigator for SisterTalk Hartford, a randomized study aimed at improving “the engagement of African-American women to lose weight and attain a healthy lifestyle.” Dr. Fifield discussed two theoretical perspectives used to design the study. Social Action Theory, when applied to weight control, postulates that good problem solving skills are needed to achieve long-term outcomes.<sup>34</sup> This view emphasizes social interdependence and interaction. In such a program, participants set goals and take action, and it provides motivation and support. This appeals to patients and in turn helps them to develop appropriate coping strategies. To create such a program requires information about the contextual situation of the population. Rogers’ theory of Diffusion of Innovations\* explains how, why, and at what rate new ideas and technology spread through cultures. The study organizers applied this theory to improve adoption of the program, for which it must be easy to understand, better than previous ideas and, most importantly, adaptable. A flexible approach is more engaging and encourages participation.

Aspects of these theories were brought together to create SisterTalk, a faith-based, church-based healthy lifestyle program. When designing the study, many cultural and social issues specific to African-American women were considered. The initial phase of the study was carried out in Boston. The focus group found that many Black women want to weigh less, but do not view themselves as unattractive. They worry about losing weight in the “wrong places” and are not focused on a slim figure. In response, the SisterTalk program concentrated on “healthy eating” and “getting to your best body,” and de-emphasized weight loss. There was no specific weekly target, and they allowed for multiple criteria for success.

It was important that the women have ownership, so all aspects of the film-based program were written and acted by Black women, and African inspired art and dance were used as symbols for the program. The focus group participants also expressed a desire to engage with program leaders as peers – “sister-to-sister” – and have real-life testimonials rather than traditional lesson-type learning. The women identified strongly as caregivers, so SisterTalk emphasized that in caring for themselves, the women were caring for others.

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\* Popularized by Everett Rogers in his 1962 book, *Diffusion of Innovations*.



## SISTERTALK HARTFORD

Hartford was chosen as the site for the translational phase of the study, a partnership among twelve churches, two universities and a general hospital. A user-friendly kit was provided to participants, and the community based participatory research approach promoted trust. Each of the twelve sessions in the program blended science with faith to inspire the women to achieve their goals.

The group leader would begin sessions with a sermonette introducing the theme. Scenes from the SisterTalk films were presented, followed by reflection and discussion. Many of the sessions utilized a biblical passage or parable as a theme to connect the women's spirituality with their healthy lifestyle. An example from the "Setting Goals" session:

*I press on toward the goal to win the prize for which God has called me heavenward. (Philippians 3:14)*

Participants were recruited from pulpit and church circular announcements, and sign-ups were conducted at church-based information sessions. Eligibility screening was done by phone, while interviews and measurement sessions were in-person. Following the initial measurement sessions, lead pastors were randomly assigned to control or intervention groups. Control groups were given healthy lifestyle films without the SisterTalk approach.

## STUDY OUTCOMES

Women in the  
SisterTalk  
intervention  
group were **2.5**  
times more likely  
to have  
**reduced**  
their **BMI**.<sup>35</sup>

Of the women who were initially contacted to participate in SisterTalk Hartford, 76% (315 participants) signed up and 85% stayed through fifteen months. Of the control group, only 70% stayed for that same duration. The primary outcomes examined were dietary and activity change, waist circumference, weight, and Body Mass Index (BMI), while secondary outcomes were self-efficacy and social support. Women in the intervention group were 2.5 times more likely to have reduced their BMI.<sup>35</sup> Interestingly, many of the groups, both control and intervention, initiated walking groups, but despite the addition of exercise to the programs, SisterTalk intervention remained significantly more effective at reducing BMI.

SisterTalk Hartford resulted in significant weight loss, sustained for an average of ten months after completing the program. This outcome is promising compared to other weight loss programs. Through the study, the investigators developed food habit questionnaires that have proven reliable for evaluating dietary change.<sup>36,37</sup> The research also uncovered a low prevalence of fat-lowering behaviors and healthy eating habits in African-American women, emphasizing the importance for a culturally appropriate intervention.<sup>38</sup> SisterTalk was later adapted for delivery to Black women via cable television.<sup>39</sup>

<sup>34</sup> Kumanyika S. K. and Ewart C. K. Theoretical and baseline considerations for diet and weight control of diabetes among blacks. *Diabetes Care*. 1990 Nov; **13**(11):1154-62.

<sup>35</sup> Data presented by J. Fifield in "Dialogues on Diversifying Clinical Trials," Washington, D.C., 2011 Sept 23.

[http://www.womenshealthresearch.org/site/PageServer?pagename=events\\_clinicaltrials](http://www.womenshealthresearch.org/site/PageServer?pagename=events_clinicaltrials).

<sup>36</sup> Risica P. M., et al. Assessing Fat-related Dietary Behaviors among Black Women: Reliability and Validity of a New Food Habits Questionnaire. *J Nutr Edu Behav*. 2007 Jul 1; **39**(4):197-204.

<sup>37</sup> Anderson C. A. M., et al. Assessing Change in Dietary-Fat Behaviors in a Weight-Loss Program for African Americans: A Potential Short Method. *J Am Diet Assoc*. 2007; **107**(5):838-42.

<sup>38</sup> Gans K. M., et al. Dietary Behaviors and Portion Sizes of Black Women Who Enrolled in SisterTalk and Variation by Demographic Characteristics. *J Nutr Edu Behav*. 2009; **41**(1):32-40.

<sup>39</sup> Gans K. M., et al. The development of SisterTalk: a cable TV-delivered weight control program for black women. *Prev Med*. 2003; **37**(6):654-67.

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## CLINICAL TRIAL SUCCESS IN NATIVE AMERICAN POPULATIONS: LESSONS FROM THE SANDS TRIAL

### A BARRIER TO TRADITIONAL MEDICINE IN NATIVE AMERICAN CULTURE

Jeffrey Henderson, MD, MPH, an Internist and Epidemiologist, is a Lakota Sioux, and an enrolled member of the Cheyenne River Sioux tribe from North Central South Dakota. Dr. Henderson was first faced with the cultural barriers of traditional medicine when treating members of the Sioux tribe with Type 2 diabetes mellitus (DM2). DM2 is highly prevalent among the Native American population, with some groups more affected than others are. American Indians and Alaska Natives have 2.2 times greater risk for DM2.<sup>40</sup> According to Dr. Henderson, roughly 50% of South Dakota Native Americans over the age of forty have DM2, the highest incidence of the disease in the world.

Despite a clinical recommendation for insulin treatment, these patients were reluctant to start on insulin, based on their cultural tradition against breaking the skin outside of tribal ceremony. Inhalable insulin was in early trials at the time, and Dr. Henderson seized the opportunity to introduce the trial to his community.

### THE SANDS TRIAL

In 2001, a group of investigators, including Dr. Henderson, received funding from the National Heart, Lung and Blood Institute (NHLBI) to conduct the SANDS (Stop Atherosclerosis in Native Diabetics) trial.<sup>41</sup> The rigorous, randomized-control trial was aimed at aggressively lowering cholesterol and blood sugar to the usual care standard in Native American diabetics.

The study enrolled 499 Native American men and women over the age of forty, all with DM2 and a history of high cholesterol or high blood pressure.<sup>42</sup> Participants were randomized to receive statins alone (standard treatment) or statins plus ezetimibe (aggressive treatment). In a three-year follow-up of the trial, Dr. Henderson and colleagues found that participants in the aggressive treatment group showed reduced carotid artery thickness.<sup>43</sup> When they published the findings in 2008, they became one

of only five or six groups worldwide who have demonstrated significant reversal of carotid artery thickness (compared to halting or slowing progression of thickening), a result Dr. Henderson said is not achieved in most major cholesterol inhibitor trials.

#### LESSONS LEARNED

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The study was one of the first to be carried out fully within the Native American population, and all four sites were incorporated within the Indian Health Service (IHS) hospitals or clinics. Dr. Henderson feels this was crucial to the success of the trial, that it was incorporated “so well into the place where the people usually receive their [health] care.” IHS is part of the U.S. Department of Health and Human Services (HHS) and serves over 1.3 million American Indians living on or near reservations.

Dr. Henderson also highlighted the ethical issues surrounding clinical trials conducted within the Native American community, wherein the issue of group consent is needed in addition to individual consent. He received tribal approval at his site. The facility was not located on a reservation so this was not required; however, it increased awareness of the trial and likely contributed to higher enrollment.

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<sup>40</sup> *Indian Health Service* [Internet]. “Facts-at-a-Glance: Diabetes in American Indians and Alaska Natives.” Rockville, MD: Indian Health Service; Copyright 2011. Available from: [http://www.ihs.gov/MedicalPrograms/Diabetes/index.cfm?module=resourcesFactSheets\\_AIANs08](http://www.ihs.gov/MedicalPrograms/Diabetes/index.cfm?module=resourcesFactSheets_AIANs08). [Updated: 2011; Accessed: 2012 Jan 13].

<sup>41</sup> Howard B. Stop Atherosclerosis in Native Diabetics Study (SANDS). In: [www.ClinicalTrials.gov](http://www.ClinicalTrials.gov) [Internet]. Bethesda (MD): National Library of Medicine (U.S.). [Updated: 2009 Feb 4; Accessed: 2011 Nov 3]. Available from: <http://clinicaltrials.gov/ct2/show/NCT00047424>. Identifier: NCT00047424

<sup>42</sup> Fleg J. L., et al. Effect of Statins Alone Versus Statins Plus Ezetimibe on Carotid Atherosclerosis in Type 2 Diabetes: The SANDS (Stop Atherosclerosis in Native Diabetics Study) Trial. *J Am Coll Cardiol*. 2008; **52**(25):2198-205.

<sup>43</sup> Howard B. V., et al. Effect of Lower Targets for Blood Pressure and LDL Cholesterol on Atherosclerosis in Diabetes. *JAMA*. 2008; **299**(14):1678-89.

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## NATIONAL MINORITY AIDS COUNCIL: DIALOGUE ON DIVERSITY

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### FOSTERING TRUST

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The lingering minority distrust of the medical/research communities stems from the long history of ethics and civil rights violations with medical experiments and clinical trials. This is especially prevalent among older members of the community, who can hold great influence over the local population.

In order to engage these groups, “local influences” must be taken advantage of, especially community leaders. Regardless of their role in the community, these leaders once educated on the nature of the research and goal of the trial can be highly

“If the **CAB** is not on board... you’re going to have a hard time for **recruitment** into your clinical trial.”

-Daniel Montoya, Deputy Executive Director, National Minority AIDS Council

influential in ensuring enrollment of a diverse population. Following the study, the same leaders should be made aware of the outcomes and they should have an understanding and appreciation for the role they played in the process.

The National Minority AIDS Council (NMAC) has a mission to develop leadership in communities of color to address the challenges of HIV/AIDS through a variety of public policy education programs; national conferences; treatment and research programs and trainings; electronic and printed resource materials; and an informational website.

#### ENGAGING COMMUNITY ADVISORY BOARDS

Daniel Montoya, Deputy Executive Director of NMAC, emphasized the importance of Community Advisory Boards (CABs): “If the CAB is not on board...you’re going to have a hard time for recruitment into your clinical trial.” To best engage CABs, they should be fully representative of the community. They can be a sponsor’s biggest ally in bringing a particular population into a study. Furthermore, literacy is paramount; the HIV/AIDS community is generally well-informed. Patients must understand fully their involvement in the trial.

#### FACILITATING BROADER MINORITY PARTICIPATION

While trust is a major factor in recruiting minorities to enroll in clinical trials, there are practical barriers. Minorities may be willing to participate, but for many patients, obtaining or funding transportation and childcare can be significant obstacles. According to Montoya, this is particularly true for women of color. Knowledge of clinical trials is also essential, as many minorities are not aware of the clinical trials being conducted in their community. Increased marketing must be targeted more specifically within these communities. Montoya says, “It’s really important ...to make sure that [CABs] are not only working with you to recruit into that clinical trial, but they’re working to recruit a very diverse population.”

## BEYOND THE IVORY TOWER: CLINICAL TRIALS FOR ALL

**GARY PUCKREIN, PHD**, is President and CEO of the National Minority Quality Forum and Executive Director of the Alliance of Minority Medical Associations.

### THE NATIONAL CLINICAL TRIAL NETWORK

#### THE ZIP CODE ANALYSIS PROJECT

Gary Puckrein, PhD, is President and CEO of the National Minority Quality Forum (NMQF). NMQF was founded in 1998 to strengthen the ability of communities and policy-makers to eliminate the disproportionate burden of premature death and preventable illness in special populations through evidence-based, data-driven initiatives.

The Zip Code Analysis Project (ZCAP) is a comprehensive database that links demographic, environmental, claims data, clinical laboratory values, and other data elements into one centralized data warehouse, linked by zip code.<sup>44</sup> The data revealed that of the approximately 38,000 zip codes in the United States, 70% of all African-Americans live in just 3,000 of these areas; Hispanics are slightly more spread out. By linking health statistics at a zip code level, they have been able to map chronic diseases as they occur throughout the country. They have used 800 million patient records and partnered with over a dozen pharmaceutical companies to develop a number of disease atlases, some of which include:

- ◆ Mapping Lung Cancer ([www.maplungcancer.com](http://www.maplungcancer.com))
- ◆ U.S. Diabetes Index ([www.usdiabetesindex.com](http://www.usdiabetesindex.com))
- ◆ U.S. HIV/AIDS Index ([www.maphiv.org](http://www.maphiv.org))
- ◆ Hepatitis C Index ([www.maphepc.com](http://www.maphepc.com))
- ◆ Tracking MRSA (methicillin-resistant *staphylococcus aureus*; [www.mapmrna.org](http://www.mapmrna.org))
- ◆ PAD Atlas (peripheral arterial disease; [www.mappad.org](http://www.mappad.org))
- ◆ Z-Atlas (tracking chronic kidney disease, diabetes, cardiovascular disease, HIV/AIDS, peripheral arterial disease, and clinical trials; [www.z-atlas.com](http://www.z-atlas.com))

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#### THE NATIONAL CLINICAL TRIAL NETWORK

While working on these maps, NMQF decided to overlay clinical trial data. Dr. Puckrein reported that about one-third of all trials are conducted in regions of the country with predominantly minority populations. Recognizing the lack of an overarching national infrastructure for clinical trials, NMQF designed the National Clinical Trial Network (NCTN).

NCTN is a warehouse for data – a virtual library of maps, charts, graphs, and industries – containing information about patterns of illness (prevalence, outcomes, cost, etc.). NCRN analyzes how diseases afflict populations by geography, race and ethnicity, gender, age, and time. The network also provides an outlet for interactive communication to link researchers to physicians who are practicing in communities where potential diverse candidates for clinical trials reside.

The NCTN data warehouse includes:

- ◆ Disease database – 800,000,000 patient records
- ◆ Clinical trial database – 300,000 clinical trial sites
- ◆ Physician static database – 800,000 clinicians
- ◆ Physician interactive database – arriving in 2012

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#### NCTN AS A TOOL FOR CLINICAL TRIAL RECRUITMENT

The purpose of NCTN is to accelerate the recruitment into clinical trials of a representative sample of consumers who are anticipated to benefit from a proposed

therapy. It views the patient as a consumer. According to Dr. Puckrein, “If you have a chronic disease, or indeed any disease, there are certain products and services that you need to consume...in order to manage that disease and get a cure.” Thus, clinical trials should be focused on the population that would most employ that service, and use that population to test the validity of the product.

The static physician database provides contact information, but the coming interactive database will facilitate email communication. For instance, a sponsor initiating a trial for a diabetes treatment will be able to contact, all at once, every registered endocrinologist across the country to let them know about the trial and inquire as to their interest in participating and/or if they have any patients eligible for the study. As a result, thousands of physicians could potentially respond to the request. From this, sponsors will be able to expedite recruitment into clinical trials.

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<sup>44</sup> “Profiling the Health Status of Minority Communities by ZIP Code,” funded by a grant from the National Association for Elimination of Health Disparities (Washington D.C.), awarded 2002 Jun 21.

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## IMPROVING REPRESENTATION OF DIVERSE PATIENTS IN CLINICAL TRIALS

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### LILLY’S COMMITMENT TO CLINICAL DIVERSITY

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The mission of Eli Lilly is to make medicines that help people live longer, healthier, more active lives. The historical approach to drug development has been “one-size-fits-all”; Lilly is moving away from this model towards tailored therapeutics. Their goal is to improve patient outcomes and health outcome predictability through tailoring the drug, dose, timing of treatment, and relevant information.

Coleman Obasaju, MD, PhD, Senior Medical Director at Eli Lilly, echoed the sentiments of other speakers, expressing his dismay over the striking disparity between cancer trial populations and the prevalence of cancer among racial groups. Caucasians are greatly overrepresented in clinical trials relative to prevalence of disease. Eli Lilly has thus initiated a cross-functional approach to ensure that representation of minorities in clinical trials matches numbers in disease prevalence by race and ethnicity. Improvements have been made for African-American representation, but less so for Hispanics.

### STRATEGY FOR DIVERSITY

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Eli Lilly’s strategy for increasing clinical diversity involves looking earlier and more often for medically relevant differences in drug response. They are consistently considering a

broader range of data sources, assessing heterogeneity of response, and using data that indicates non-response to inform future research strategies.

Secondly, Eli Lilly is making efforts to increase enrollment of diverse patients specifically in Phase III<sup>\*</sup> and Phase IV trials.<sup>†</sup> Their objective is to collect, analyze, and disclose specific demographic information and collect race sub-category data for these trials. This is particularly important in Phase IV, wherein the product has already been approved and released, and is in distribution to the patient populations who will most use the drug. Eli Lilly has located 229 new diverse clinical trial sites, with an aim for two new diverse sites added per eligible trial. All patient materials are proactively being translated into Spanish.

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#### COMPLEX PROBLEMS REQUIRE PARTNERSHIPS

To increase awareness of the need for diverse patients and investigators, Eli Lilly has collaborated with the National Medical Association (NMA), the National Hispanic Medical Association (NHMA), and the Education Network to Advance Cancer Clinical Trials (ENACCT). A Latino Advisory Board gave Lilly strong feedback, which they are applying to create culturally competent tools.

Lilly researchers observed they had little minority data for an already-approved drug for non-small cell lung cancer (NSCLC), so they carried out a prospective observational study to assess impact of race and ethnic origins on outcomes and resource utilization. Their goals were to examine data from 400 Caucasians, 200 African-Americans, 200 Hispanics, and 200 Asians. Obtaining the numbers was far more difficult than they expected, and the maximum number of African-Americans they were able to enroll was 65, the minimum needed for meaningful statistical analysis. They discovered the barriers to enrolling minority patients were lack of awareness of clinical research, lack of acceptance, and language barriers. Dr. Obasaju said they are “learning on the fly” and “adapting as [they] go” to incorporate the best methods for increasing minority enrollment.

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#### LEARNING FROM MINORITIES TO RECRUIT MINORITIES

Eli Lilly has assembled advisory boards made up of oncologists in the U.S. and the European Union to gain feedback on diversity. One of the major lessons in the improvement of enrollment diversity was the necessity for minority investigators. In their project, “Reducing Disparities in Access to Oncology Clinical Trials” Lilly assessed the impact of protocol design or “Informed Consent Documents (ICDs)” on diverse

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<sup>\*</sup> Includes 300 to 3,000 patients; conducted after preliminary evidence suggesting effectiveness of the drug has been obtained; intended to gather additional information to evaluate the overall benefit-risk relationship of the drug and provide adequate basis for physician labeling.

<sup>†</sup> Also known as “surveillance” trials; post-marketing studies to delineate additional information including the drug’s risks, benefits, and optimal use.

enrollment. A survey of site investigators and coordinators revealed the most significant barriers to enrolling diverse populations:

- ◆ Insurance status
- ◆ Patient inconvenience costs
- ◆ Availability of transportation
- ◆ Distance to the study site
- ◆ Patient and family concerns about risk

Eli Lilly identified the necessary steps to improve the process of recruiting minorities. First, they now require that protocol templates include information on ethnic differences, considerations, and enrollment goals. Second, each trial site is assessed to ensure they have personnel who speak the relevant local language, and that site staff are educated on the potential barriers and solutions for diverse, elderly, and other underserved patients. They have initiated a Patient Navigation project to train patient navigators on clinical trials to address financial and logistical barriers.

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## ACCESSING CLINICAL TRIALS: A PATIENT'S PERSPECTIVE

### ZORA BROWN, CANCER SURVIVOR

Zora Brown is a 28-year survivor of breast cancer and an ovarian cancer survivor. She has served on the board for the National Cancer Institute and is the founder of "Rise, Sister, Rise", a model for support groups for African-American women with breast cancer.

Four generations of Ms. Brown's family have suffered through breast cancer, and all are avid proponents of clinical trial participation. Brown's mother told her, "If we don't participate in clinical trials, we are going to leave the solutions to those who do, and we may not like what we get." Brown herself has been advocating for clinical trial research for over thirty years.

Living in Washington, D.C., and later, Indianapolis, Brown was fortunate to have access to clinical trials, excellent doctors, and state-of-the-art treatment facilities in her fight

"If we don't **participate** in **clinical trials**, we are going to leave the **solutions** to those who do, and we may not like what we get."

-Zora Brown, quoting her mother, a cancer survivor



against breast cancer. Brown returned to her hometown of Oklahoma City six years ago. She said she was impressed with the quality of healthcare there. Three years later, she was diagnosed with Stage III ovarian cancer. Her initial treatment plan included the same drugs that were effective in treating Stage IV ovarian cancer in her older sister. These happened to be taxol (Paclitaxel®) and platinum drugs,\* which her sister received when enrolled in clinical trials for the treatments.

#### GAINING ACCESS TO CANCER TRIAL DRUGS

Unfortunately, the treatment was unsuccessful, as were a series of others. Brown said, “I took every drug you can imagine.” Her oncologist recommended oncotyping, a test which examines tumor cells on a molecular level to better characterize the type of tumor which can help tailor treatment for the individual. Together, Brown and her oncologist discovered a poly (ADP-ribose) polymerase (PARP) inhibitor, which according to Brown “looked like it was designed for me.” However, there were no trials for the drug ongoing in Oklahoma.

Brown utilized the wealth of contacts she had gained over the years to try to find out how she could get the treatment that could save her life. She received information about where PARP inhibitor trials were being held and who to call, but nothing in Oklahoma. Through a very fortuitous series of contacts, which included a pharmaceutical sales representative, her oncologist, an IRB, and friends at FDA, Brown had access to the drug within a month. That was three years ago, and she has been on it ever since.

#### INTEGRIS CANCER INSTITUTE

Brown is now on the IRB for the INTEGRIS Cancer Institute of Oklahoma, and is addressing the issues that keep patients from gaining access to trials, one of which is a heavy financial burden. She says, “I understand why people don’t participate in clinical trials.” On top of the cost of filling her gas tank for the 50-mile round trip she makes five days a week to receive treatment, Brown isn’t reimbursed for other costs such as the chemo chair, or heparin; only the drugs are free. Money is not necessarily the answer, but there must be a solution to offset some of the costs associated with a clinical trial.

Brown is active on health boards across her community, both locally and nationally. She advocates for streamlining the clinical trial process, and educating and involving patients. Brown says, “There is care to be given beyond Washington, D.C., beyond the

“There is **care** to be  
given **beyond**  
**Washington,**  
**D.C.,** beyond the  
areas where we think  
the **best**  
**science** is  
practiced.”

-Zora Brown, INTEGRIS Health

\* Platinum-containing anti-cancer drugs include cisplatin (Platinol®, Platinol-AQ®), carboplatin (Paraplatin®, Paraplatin-AQ®), and oxaliplatin (Eloxatin®, Oxaliplatin Medac®).

areas where we think the best science is practiced.” She encourages trial sponsors to come to Oklahoma. INTEGRIS Health, Oklahoma’s largest healthcare provider, built the INTEGRIS Cancer Institute of Oklahoma in 2009. Patients have come from 25 states and 5 countries, and more than 1,800 patients are seen each month. Oklahoma has quality healthcare and a diverse population, making it an ideal site for clinical research.

## STRATEGIES IN CLINICAL TRIALS: RESEARCH DESIGN FOR RECRUITMENT, RETENTION, ANALYSIS

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ARMIN WEINBERG, PHD, is CEO of the Life Beyond Cancer Foundation and Clinical Professor at the Baylor College of Medicine.

### A BEST PRACTICE: REQUIRING AND IMPLEMENTING POLICIES THAT INCLUDE PARTICIPANTS

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#### THE EDICT PROJECT

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Armin Weinberg, PhD, discussed the Eliminating Disparities in Clinical Trials (EDICT) project, the first to comprehensively examine opportunities to make a difference through policy changes. The multi-sector approach incorporates analysis of different diseases, phases of trials, and the role of industry, government, and research institutions. EDICT brought together a wide variety of stakeholders to identify the top priorities for policy recommendations to influence clinical trial diversity.

The EDICT group operated on the beliefs that: all individuals are entitled to participate in clinical trials, participants and researchers must understand and promote the benefits of clinical trials, and results from clinical research will benefit the participants’ communities and societies at large. The methodology for the EDICT teams consisted of policy process questions:

- ◆ What is the problem? How does it manifest itself?
- ◆ What would success look like?
- ◆ Whose behavior needs to change in order to achieve the goal?
- ◆ Who has the ability to change the behavior of the target audience?
- ◆ What policy is recommended to achieve the behavior change in the target audience?
- ◆ What is the feasibility of this policy?
- ◆ What is the underlying thinking on why this policy will be effective?

The groups outlined in the EDICT model are the underrepresented participants and other groups with various levels of interest, ranging from participating and supporting stakeholders to regulating and influencing stakeholders. Dr. Weinberg stressed there is nothing that any one group can do alone; rather a “systems approach” must be taken. He says there is a role for everyone to play going forward: “Whether you are a research

organization, a pharmaceutical company, an academic researcher or an advocate, you have the opportunity to take on something.”

#### SPECIFIC ISSUES IN NEED OF CHANGE

One example Dr. Weinberg provided was a report on “the signaling effect.” The EDICT Publications Working Group examined how to effect change by changing policy on publications. In other words, if journals require a more stringent analysis of trial data by subpopulation, researchers will be forced to include more women and minorities in trials and analyze the data accordingly. The group identified three aspects necessary for change: guidelines for reviewers to examine submissions with clinical trial data, guidelines for the authors, and sample language to explain why the paper was rejected if they did not include representation of these populations in their studies. EDICT responded accordingly with solutions. They also concluded that cost should not be a barrier in clinical trials.

Limited English Proficiency (LEP) negatively affects a patient’s access to health services and quality of the healthcare he or she receives, and often results in his or her exclusion from clinical trials. For those LEP patients that do participate in trials, existing data suggests that they can suffer from shortcomings in ethical, legal, and scientific standards.<sup>45</sup> Language barriers make LEP patients vulnerable to coercion or undue influence or adverse events due to miscommunication between physicians and patients.<sup>46</sup>

In summary, the important factors being addressed by EDICT are the quality of research, social justice, and the business case. Dr. Weinberg concluded by saying, “Science is changing and there’s going to be an opportunity for us to do a lot more.”

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<sup>45</sup> Bustillos D. Limited English Proficiency and Disparities in Clinical Research. *J Law Med Ethics*. 2009; **37**(1):28-37.

<sup>46</sup> Flores G., et al. Errors in medical interpretation and their potential clinical consequences in pediatric encounters. *Pediatrics*. 2003; **111**(1):6-14.

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## SUCCESSFUL ENROLLMENT OF WOMEN IN AN HIV CLINICAL TRIAL: THE GRACE STUDY EXPERIENCE

### THE GRACE STUDY

Joseph Mrus, MD, MSc, gave a lesson on clinical trial design based on the GRACE (Gender, Race and Clinical Experience) study. GRACE was a multi-center, open-label Phase IV trial conducted by Tibotec Therapeutics (a division of Centocor Ortho Biotech Products, L.P.) that compared gender differences in the efficacy, safety, and tolerability of an antiretroviral treatment for HIV-1-infected men and women.<sup>47</sup>

Despite research suggesting sex-based differences in drug efficacy, toxicity, and tolerability profiles, women have been underrepresented in HIV clinical trials.<sup>48</sup> Of the total number of women in the U.S. with HIV/AIDS, over 80% are African-American or Hispanic, and outcomes in women with HIV are usually worse for women of color.<sup>49</sup> Phase III trials of an antiretroviral treatment included mostly gay white men, but an advisory board ruled that 10% female enrollment was unacceptable. GRACE became the Phase IV study for this treatment, with a primary objective of recruiting greater numbers of women, and a secondary goal of recruiting minorities.

### MEANS TO INCREASE ENROLLMENT DIVERSITY

What did Janssen do to ensure more diverse enrollment? Significant early planning was key, including research of past trials. As part of a media campaign, the butterfly logo (Figure 2) was carefully designed to brand the project and increase recognition while retaining anonymity for the study (i.e., not identified as HIV/AIDS). Social workers were involved to help patients feel at ease and help them understand the importance of the trial. According to Dr. Mrus, “the community sold the community.”



**Figure 2. The butterfly logo was critical in branding the GRACE study.**

The GRACE study aimed to enroll at least two-thirds women. It was a success; halfway through the study, male enrollment was only 10%. In November 2007, only a year after recruitment began, GRACE investigators reached their enrollment target of 420 patients. More than half of female GRACE participants were Black women, a proportion that closely mirrors that of the American population living with HIV/AIDS (Figure 3, page 34).<sup>50,51</sup> Dr. Mrus admits the study may have focused too much on recruitment and too little on retention, as Black women also had the highest dropout rate. The study revealed both gender-based and race/ethnicity-based differences.<sup>52</sup> A greater number of women than men dropped out of the study, as

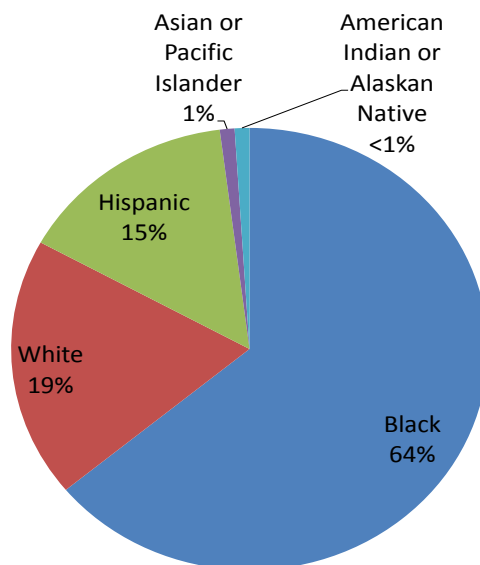
**80%** of  
women in  
the U.S. with  
HIV or AIDS  
are African-  
American  
or  
Hispanic.<sup>49</sup>

did Black women compared to Whites. Women had a higher rate of adverse events, but African-Americans had higher rates of virologic failure.<sup>53</sup>

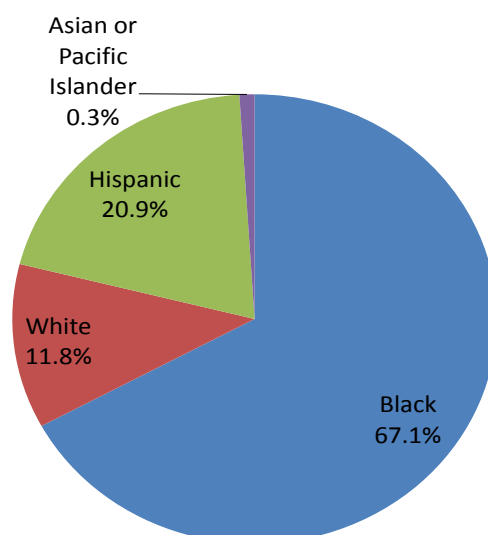
#### STRATEGIES FOR SITE OUTREACH AND PATIENT SUPPORT FOR THE GRACE STUDY

The sponsors of the GRACE study held an investigator meeting to identify site-specific requirements and recruitment plans. A major strategy was to select sites that focused on the needs of women. Other methods used for increasing enrollment, retention, and outcome included and site-specific enrollment plans and on-site support meetings. Study sites were targeted to areas with high proportions of HIV/AIDS cases in females (58 in the U.S., 4 in Canada, and 3 in Puerto Rico). Because doctors in these areas were not as experienced, special mentoring was included for novel sites. Sites with no experience were better able to focus on the study than more experienced investigator groups. Consequently, study sites with less experience outperformed practiced study groups.

**Women living with HIV/AIDS in the US**  
**n = 131,195**



**Women enrolled in GRACE**  
**n = 287**



**Figure 3. Race/ethnicity of women in GRACE is representative of current trends in HIV/AIDS cases among women and communities of color in the US.**<sup>54,55</sup>

The sponsors sought to reduce barriers to care, and part of doing so included funds for travel, food, and daycare. In addition, they provided not only the study drug, but also all

the HIV/AIDS medications, in order to comprise a successful regimen. This included etravirine (Intelence®), an as-yet-unavailable experimental antiretroviral drug. They also provided supplemental site grants for patient support activities, and helped to increase flexibility and availability of healthcare practitioners at study sites. At the end of the study, they coordinated with the sites to ensure that participants were informed of the results, and followed up with each site a year and a half later with surveys to gain more feedback on successful aspects of the study and to identify areas for improvement. Overall, GRACE is a highly successful model for the recruitment of women and minorities in clinical trials, but room remains for expansion in participant retention.

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<sup>47</sup> Tibotec. GRACE: A Study to Compare the Effectiveness, Safety and Tolerability of PREZISTA (Darunavir)/Ritonavir by Gender and Race When Administered with Other Antiretroviral Medications in Human Immunodeficiency Virus (HIV) Positive Women and Men. In: [www.ClinicalTrials.gov](http://www.ClinicalTrials.gov) [Internet]. Bethesda (MD): National Library of Medicine (U.S.). [Updated: 2011 Jan 13; Accessed: 2011 Nov 7]. Available from: <http://www.clinicaltrials.gov/ct2/show/NCT00381303?term=grace+tibotec&rank=1>. Identifier: NCT00381303

<sup>48</sup> Kremer H. and Sonnenberg-Schwan U. Women Living with HIV Does Sex and Gender Matter? A Current Literature Review. *Eur J Med Res*. 2003 Jan 28; **8**(1):8-16.

<sup>49</sup> *Centers for Disease Control and Prevention* [Internet]. "HIV Surveillance by Race/Ethnicity (through 2009)." Atlanta, GA: U.S. Department of Health and Human Services; Copyright 2012. Available from: <http://www.cdc.gov/hiv/topics/surveillance/resources/slides/race-ethnicity/index.htm>. [Updated: 2011 Apr 28; Accessed: 2012 Jan 13].

<sup>50</sup> *Centers for Disease Control and Prevention* [Internet]. "HIV/AIDS Surveillance Report." Atlanta, GA: U.S. Department of Health and Human Services; Copyright 2012. Available from: <http://www.cdc.gov/hiv/topics/surveillance/resources/reports/>. [Updated: 2012 Jan 10; Accessed: 2012 Jan 11].

<sup>51</sup> Falcon R., et al. Recruitment and Retention of Diverse Populations in Antiretroviral Clinical Trials: Practical Applications from the Gender, Race And Clinical Experience Study. *Journal of Women's Health*. 2011 Jun 10; **20**(7):1043-50.

<sup>52</sup> Feinberg J., et al. Health-Related Quality of Life in the Gender, Race, and Clinical Experience Trial. *AIDS Res Treat*. 2011.

<sup>53</sup> Data presented by J. Mrus in "Dialogues on Diversifying Clinical Trials," Washington, D.C., 2011 Sept 22. [http://www.womenshealthresearch.org/site/PageServer?pagename=events\\_clinicaltrials](http://www.womenshealthresearch.org/site/PageServer?pagename=events_clinicaltrials).

<sup>54</sup> *Centers for Disease Control and Prevention* [Internet]. "HIV/AIDS Surveillance Report." Atlanta, GA: U.S. Department of Health and Human Services; Copyright 2012. Available from: <http://www.cdc.gov/hiv/topics/surveillance/resources/reports/>. [Updated: 2012 Jan 10; Accessed: 2012 Jan 11].

<sup>55</sup> Falcon R., et al. Recruitment and Retention of Diverse Populations in Antiretroviral Clinical Trials: Practical Applications from the Gender, Race And Clinical Experience Study. *J Womens Health*. 2011; **20**(7):1043-50.

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## MYTHS AND REALITIES REGARDING THE PARTICIPATION OF ETHNIC MINORITIES IN CLINICAL TRIALS

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### RACE AND ETHNICITY IMPACT DRUG RESPONSE AND DISEASE INCIDENCE

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Alfonso Alanis, MD, began his discussion with several examples of different effects of drugs among minorities and genders. These include rosuvastatin (Crestor®), of which Asians are more sensitive and must be started on a lower dose,<sup>56</sup> while African-Americans are less responsive and require a higher dose. Aricept® (Pfizer), on the other hand, is slightly more effective at treating the symptoms of Alzheimer's disease in African-Americans.<sup>57</sup> Other drugs with varying effects across racial and ethnic groups are aspirin, gefitinib (Iressa®), hydralazine/ isosorbide dinitrate (Bi-Dil®),<sup>\*</sup> veliflapon (DG-031®), and amlodipine/valsartan (Exforge®).<sup>†</sup>

The most important diseases that disproportionately affect ethnic minorities include type 2 diabetes (DM2), cardiovascular diseases (hypertension, stroke, etc.), infectious diseases (HIV/AIDS, STDs), some types of cancer (colon, prostate, cervix, lung) and neuropsychiatric illnesses (schizophrenia, depression, bipolar disorder). The racial and ethnic demographics of patients participating in clinical trials for treatment for these diseases are not representative of disease incidence (Figure 4, page 37).<sup>58,59</sup>

### FACTORS WHICH IMPACT MINORITY ENROLLMENT

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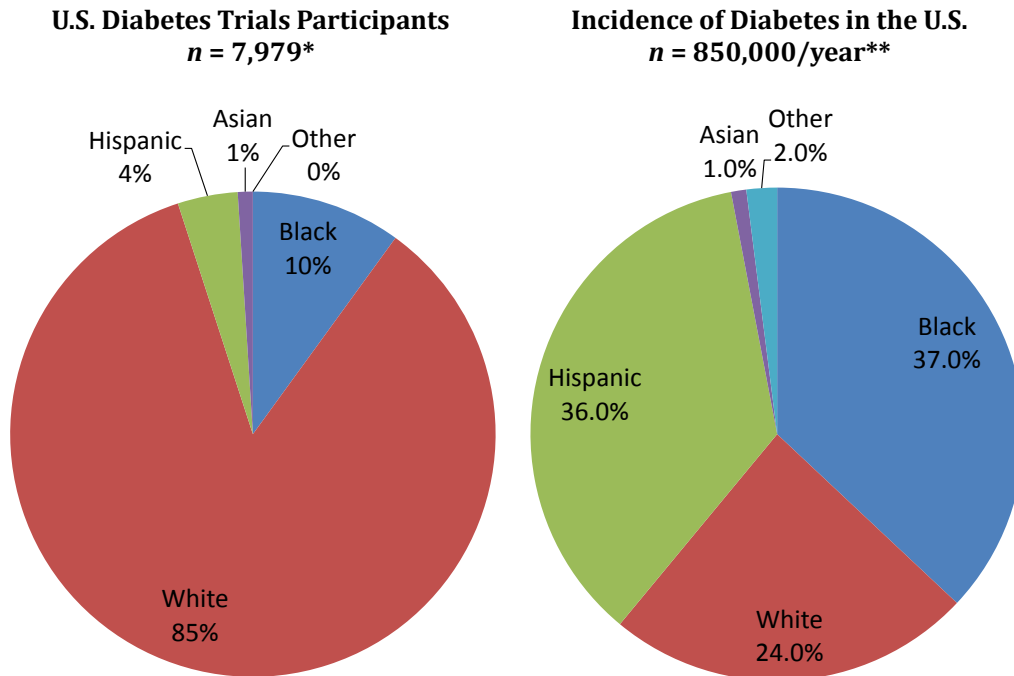
There are many reasons for the discrepancy in disease incidence versus clinical trial population. The factors rely on both patients and sponsors. Dr. Alanis outlined the top ten reasons why minorities do not participate in clinical trials:

1. Mistrust in healthcare system, lack of consent
2. It will delay the clinical trial
3. Retention is poor
4. Compliance is poor
5. It will add complexity
6. It will add significant cost
7. Do not have the time (childcare, lost wages, etc.)
8. Language barriers (Hispanics, Asian, others)
9. Ignorance/lack of education
10. Cultural attitudes

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<sup>\*</sup> Bi-Dil® is a proprietary combination of hydralazine (Apresoline®) and isosorbide dinitrate (Dilatrate®).

<sup>†</sup> Exforge® is a proprietary combination of amlodipine (Norvasc®) and valsartan (Diovan®).



**Figure 4. Disparity between U.S. diabetes trials participants and incidence (new cases) of diabetes.** \*FDA data, 1998-2001; represents 80% known diabetes trial participants.<sup>60</sup> \*\*New cases in the U.S. in 2005.<sup>61</sup>

In 2006, Wendler and colleagues published an analysis of twenty health research studies that reported consent rates by race or ethnicity.<sup>62</sup> The study revealed very small differences in the willingness of minorities (primarily African-Americans and Hispanics) to participate in health research compared to Caucasians. Thus, access to clinical trials may be of greater importance to minority recruitment. Engaging minority medical professionals is vital, as these minority physicians are more influential in providing healthcare for underserved populations.<sup>63</sup>

#### ANACLIM'S ACHIEVEMENTS AND OBSERVATIONS

In industry-sponsored studies in the U.S., investigators enroll approximately 0.3 patients per site per month. Anaclim's investigators have excelled in this respect, enrolling an average of 0.8 patients per site per month, with numbers up to 1.8 to 2 patients per month. Dr. Alanis presented data from ten DM2 trials run by Anaclim in 2006-2010. Of the 1,162 patients recruited, the majority of enrollment targets were met at least two months in advance of the start of the study. In these same studies, racial and ethnic representation was in close proportion to disease incidence in the U.S. Anaclim's experience showed that retention of minorities was similar to that of non-minorities, as was compliance. Costs averaged about 3% higher to recruit greater numbers of minorities, mainly due to extensive translation services for numerous languages, e.g., Spanish, Vietnamese, Chinese, Korean).



"If you invite  
[minorities] to  
participate,  
they will come."

-Alfonso Alanis, Majority  
Founding Partner and  
CEO, Anacim LLC

Anacim's success demonstrates that achieving diverse patient enrollment in a timely and cost-effective manner is not impossible. Minorities are too often underestimated in their willingness to participate and capacity to understand and appreciate the importance of clinical trial participation. Access to trials is the greatest obstacle. In Alanis' words, "If you invite [minorities] to participate, they will come."

<sup>56</sup> Lee E., et al. Rosuvastatin pharmacokinetics and pharmacogenetics in white and Asian subjects residing in the same environment. *Clin Pharmacol Ther.* 2005; **78**(4):330-41.

<sup>57</sup> Griffith P., et al. Safety and efficacy of donepezil in African Americans with mild-to-moderate Alzheimer's disease. *J Natl Med Assoc.* 2006 Oct; **98**(10):1590-97.

<sup>58</sup> Evelyn B., Gray K., & Rothwell R. (U.S. FDA Office of Special Health Issues): U.S. Black Participation in Clinical Trials: A Review of Selected New Molecular Entities Approved 1998-2001; Presented at the National Medical Association Annual Meeting, Honolulu, Hawaii, 2002.

<sup>59</sup> National Institute of Diabetes and Digestive and Kidney Diseases & the Centers for Disease Control. "National Diabetes Statistics Fact Sheet: General Information and National Estimates on Diabetes in the U.S". Bethesda, MD: U.S. Department of Health and Human Services, National Institute of Health, 2005.

<sup>60</sup> B. Evelyn, K. Gray & R. Rothwell (U.S. FDA Office of Special Health Issues): U.S. Black Participation in Clinical Trials: A Review of Selected New Molecular Entities Approved 1998-2001; Presented at the NMA Annual Meeting, Honolulu, Hawaii 2002.

<sup>61</sup> National Institute of Diabetes and Digestive and Kidney Diseases & the Centers for Disease Control. "National Diabetes Statistics Fact Sheet: General Information and National Estimates on Diabetes in the U.S". Bethesda, MD: U.S. Department of Health and Human Services, National Institute of Health, 2005.

<sup>62</sup> Wendler D., et al. Are Racial and Ethnic Minorities Less Willing to Participate in Health Research? *PLoS Med.* 2005; **3**(2):e19.

<sup>63</sup> Komaromy M., et al. The Role of Black and Hispanic Physicians in Providing Health Care for Underserved Populations. *New England J Med.* 1996; **334**(20):1305-10.

## FEDERAL PERSPECTIVES ON THE INCLUSION OF WOMEN AND MINORITIES IN CLINICAL TRIALS

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### PARTICIPATION IN DRUG TRIALS: FDA PERSPECTIVE

#### SEX-BASED DIFFERENCES IN HEALTHCARE NEEDS AND BIOLOGY

Ameeta Parekh, PhD, began her talk by outlining the role of women as healthcare consumers. Based on the 2010 Census, women make up almost 51% of the U.S. population. Women use the health system more, the reasons for which are longer lifespan and reproductive health and childbearing needs, as well as a higher burden for many diseases, including cardiovascular and autoimmune diseases, osteoporosis and cancer. Compared to men, women take more medication and use alternate therapies. It is thus only natural that women should be given fair consideration in clinical trials.

Dr. Parekh shared some examples of gender differences in adverse events. Torsades de pointes (TdP)<sup>\*</sup> results from QT prolongation,<sup>†</sup> and women are two to three times more likely to develop TdP than men secondary to drug therapy. Three drugs were withdrawn between 1997 and 2000 for higher incidence of TdP in women: astemizole (Himanal<sup>®</sup>), cisapride (Propulsid<sup>®</sup>), and terfenadine (Seldane<sup>®</sup>). She also shared an interesting example from a trial for the type 2 diabetes drug rosiglitazone (Avandia<sup>®</sup>), which resulted in increased incidence of fractures in women compared to men.<sup>64</sup> Overall, females have a 1.5- to 1.7-fold greater risk of developing an adverse drug reaction,<sup>65</sup> most likely due to gender-related differences in pharmacokinetic, immunological, and hormonal factors.

#### FEDERAL GUIDELINES ADDRESSING WOMEN IN CLINICAL TRIALS

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One of the first drugs to draw attention to clinical trials for women was thalidomide (Thalomid<sup>®</sup>), a sedative agent developed in the 1950s. Thalidomide was discovered to be useful in treating morning sickness in pregnant women, though soon after it was linked to significant teratogenic effects. The drug was approved for use in 1957-1962 in the U.K., Canada, Germany, and Japan, but never in the U.S. However, samples were distributed to a number of physicians in the U.S. as part of a clinical trial in which 20,000 patients received thalidomide. It was later revealed that no specific tests were done to look for possible adverse effects to the developing fetus, despite the fact that one of the indications for thalidomide was nausea and vomiting during pregnancy.<sup>66</sup> Worldwide, approximately 12,000 babies were born with phocomelia<sup>‡</sup> or other physical and mental birth defects resulting from the use of thalidomide in pregnancy.

The thalidomide tragedy led to a very conservative approach for participation of women in clinical trials and the approval of medications during pregnancy. The 1977 FDA guideline, “General Considerations for the Evaluation of Drugs” prescribed that women of childbearing potential should be excluded from the earliest dose-ranging studies, Phase I and early Phase II.<sup>67</sup> However, in 1993 FDA reversed this restriction in order to give more flexibility to Institutional Review Boards (IRBs), investigators, and patients in determining how best to ensure safety.<sup>68</sup>

More regulations were implemented in 1998<sup>69</sup> and 2000<sup>70</sup> that addressed Investigational New Drug Applications (INDs). The former of these stipulated that participants be tabulated according to age, race, and sex; the latter authorized FDA to stop studies under an IND for treatment of a life-threatening disease if women are excluded due to reproductive potential.

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<sup>\*</sup> Refers to a specific, rare variety of fatal ventricular tachycardia that exhibits distinct characteristics on an electrocardiogram.

<sup>†</sup> Increased time between the start of the Q wave and the end of the T wave in the heart’s electrical cycle. Prolonged QT interval is a biomarker for ventricular tachyarrhythmias and a risk factor for sudden death.

<sup>‡</sup> In Greek, “seal limb”; a congenital disorder characterized by underdeveloped limbs, often manifesting with ear and eye abnormalities, malformation of internal organs, retarded growth, or mental deficiencies.

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#### RECENT IMPROVEMENTS IN FEMALE ENROLLMENT AND ONGOING INITIATIVES

Women's participation in late-phase clinical trials has increased to about 50%, and there is a trend toward greater enrollment of women in early-phase trials. Most importantly, analysis of data to examine sex differences in clinical trials has increased immensely. In addition, FDA has implemented ongoing initiatives in data standardization to improve analysis of data by sex. Dr. Parekh reported that other guidelines and internal standards are in development. FDA's Sentinel Initiative will transform FDA's ability to track the safety of drugs and medical devices and, ultimately, all FDA-regulated products.<sup>71</sup> Manufacturers are required to submit Risk Evaluation and Mitigation Strategies (REMS) to ensure that the benefits of a drug or biological product outweigh its risks.

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<sup>64</sup> Kahn S. E., et al. Rosiglitazone-associated fractures in type 2 diabetes: an Analysis from a Diabetes Outcome Progression Trial (ADOPT). *Diabetes Care*. 2008 May; **31**(5):845-51.

<sup>65</sup> Zopf Y., et al. Women encounter ADRs more often than do men. *Eur J Clin Pharmacol*. 2008; **64**(10):999-1004.

<sup>66</sup> *Birth Defect Research for Children* [Internet]. "How a Commonly Used Drug Caused Birth Defects." Orlando, FL: Birth Defect Research for Children, Inc.; Copyright 2010. Available from: [http://www.birthdefects.org/research/bendectin\\_1.php](http://www.birthdefects.org/research/bendectin_1.php). [Updated: 2010; Accessed: 2011 Nov 8].

<sup>67</sup> U.S. Department of Health and Human Services, Food and Drug Administration. "General Considerations for the Clinical Evaluation of Drugs in Infants and Children". (FDA 77-3040). Washington, D.C.: U.S. Government Printing Office, 1977.

<sup>68</sup> U.S. Department of Health and Human Services, Food and Drug Administration. Guideline for the Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs. *Federal Register*. 1993 Jul 22; 58(139):39406-16.

<sup>69</sup> The Investigational New Drug Applications and New Drug Applications Regulation. *Federal Register*. 1998 Feb 1; 63:6854-62.

<sup>70</sup> Investigational New Drug Applications: Amendment to Clinical Hold Regulations for Products Intended for Life-Threatening Diseases and Conditions. *Federal Register*. 2011 Jun 1; 65:34963-71.

<sup>71</sup> *U.S. Food and Drug Administration* [Internet]. "FDA's Sentinel Initiative." Silver Spring, MD: U.S. Department of Health & Human Services; Copyright 2011. Available from: <http://www.fda.gov/Safety/FDAsSentinelInitiative/ucm2007250.htm>. [Updated: 2011 Nov 8; Accessed: 2011 Nov 8].

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## SEX/GENDER DIFFERENCES IN MEDICAL DEVICE TRIALS

### SEX-BASED DIFFERENCES IN DISEASE AND TREATMENT

Kathryn O'Callaghan discussed sex differences in the safety and efficacy of medical devices. Eight of the last ten drugs withdrawn from the market posed greater health risks to women.<sup>72</sup> FDA has been criticized for gender bias in premarket approval of cardiovascular devices, wherein sex distribution was 67% male.<sup>73</sup> While women have a higher prevalence of cardiovascular disease than men, their utilization of procedures or devices such as stents, coronal artery bypass grafts, diagnostic cardiac catheterization, and balloon angioplasty, is far lower in comparison.<sup>74</sup>

Gender-based disparities in patient representation in cardiovascular device trials favors men, but in some cases women have higher enrollment, depending on the device studied. O'Callaghan suggested that proportion of gender representation should relate to numbers on usage of the product, i.e., if more men are affected, the study should include a higher percentage of males, and vice versa. Furthermore, device trials generally have much lower sample numbers than for drug trials. This lack of data compounds the difficulty of evaluating the significance of sex differences, as there is less statistical power with which to differentiate subgroups.

The pathophysiology of the disease itself may differ by gender. Recent studies revealed that women with ischemic heart disease have less focal lesions and greater microvascular damage than men.<sup>75</sup> Focal lesions are easier to detect and more effectively treated by stent. This means that in female patients, the disease is not only harder to diagnose but also more difficult to treat. The gender differences do not excuse the lack of female representation in trials but according to O'Callaghan, "Perhaps it does somewhat explain that if women have this type of disease, they wouldn't necessarily be appropriately treated by the devices that are currently available." This reinforces the need for understanding not only health-based gender differences but also the necessity to design new treatments with these variations in mind.

### LACK OF WOMEN'S HEALTH AWARENESS AND IMPACT OF GENDER BIAS

Nationwide distribution of death rates for cardiovascular disease in women<sup>76</sup> closely mirrors that of distribution of disease incidence by race, which O'Callaghan suggests may infer a "double-whammy effect" for female minorities. Women are becoming more aware of their risk for heart disease – the number one cause of death for American women – thanks to the American

67% of  
cardiovascular  
device  
trial participants  
are men.<sup>73</sup>

Heart Association’s “Go Red for Women Campaign.”\* However, this is not reflected in the female population by race. The percentage of White women who recognize heart disease as the number one killer of females in the U.S. is a healthy 62%, but less than half of minority women – 38% of Black females, 34% of Hispanics, and 43% of others – express the same awareness.<sup>77</sup> Sadly, physicians fared worst in identifying the significant incidence of heart disease in women. Only 8% of primary care physicians, 13% of gynecologists, and a startling 17% of cardiologists were aware of heart disease as a greater cause of mortality in women than men.<sup>78</sup>

An intriguing study by Chiaramonte and colleagues examined healthcare providers’ assessment of coronary heart disease (CHD) symptoms based on gender and context of symptoms (with stress versus without stress).<sup>79</sup> Physicians were presented with hypothetical case descriptions and asked to give a diagnosis. The results were alarming. When emotional stress was reported along with symptoms of chest pain and shortness of breath, physicians were much more likely to attribute women’s symptoms as psychological in origin, rather than organic, compared to males describing the same symptoms. Speaking at the meeting, O’Callaghan said that the physicians assumed that “These women didn’t need to see a cardiologist; they needed Xanax and a psychotherapist.” The danger from this is that women with CHD may not be referred to the proper specialist by their primary care doctor, at great risk to their health.

However, stress and emotions do play a role in cardiovascular health. Of women who experienced cardiac arrest, 40% reported stress or depression before the event, compared to 16% of men.<sup>80</sup> In contrast, only 5% of women reported physical exertion prior to arrest, compared to 40% of men. Thus, the presence of stress in women does not necessarily indicate psychological origin of symptoms. Other psychosocial influences in gender bias were identified as stemming from the provider’s perception of difficulty to treat women and decreased perception of disease risk in female patients versus their heightened perception of risk of unknown treatment.

#### FDA GUIDANCE AND TRIAL CONDUCT

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Inclusion of women in clinical trials must be increased to obtain critical sex-specific data. FDA has hosted think tanks, conferences, and workshops to convene stakeholders to identify a role for FDA in the improvement of female representation in clinical trials. Their discussions with stakeholders led to new recommendations that consider the unique challenges represented in medical device research that were included in the recent draft guidance document. The goals of the FDA Center for Devices and Radiological Health (CDRH) guidance are to:

- ◆ Achieve representative enrollment – recommend strategies to enhance participation
- ◆ Collect sex-specific data – recommend statistical subgroup analyses of trial data and interaction testing

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\* [www.goredforwomen.com](http://www.goredforwomen.com).

- ◆ Introduce transparent reporting of sex-specific findings to the public

Some of FDA's recommendations for trial conduct were similar to those mentioned by other speakers, including targeting investigator sites (women's heart clinics) and engaging physicians from the trial's demographic (female investigators). CDRH is continuing to explore reasons for underrepresentation of women in device trials and is developing strategies to minimize barriers. CDRH reviewers recommend oversampling from the group most affected by the disease in question. Parallel registries for postmarket data collection will help support subgroup analysis if a sponsor is unable to obtain sufficient numbers of female (or minority) patients who meet criteria for inclusion into trials.

Only **17%** of cardiologists are aware of the **greater mortality** for heart disease in **women** compared to men.<sup>78</sup>

#### MEDICAL DEVICES PRESENT UNIQUE CHALLENGES

Some medical devices by nature have physical aspects that present issues for gender equality. The first generation of the HeartMate II Ventricular Assistance Device could not be used in women due to its size; a woman's heart/chest was simply too small to accommodate the device. The second-generation device was significantly smaller, and the trial included many more women. Thus, it was not necessarily a change in practice, but rather a change in technology, which allowed for the treatment of more women.

Advances are also being made as researchers gather evidence for sex-based physiological variations. For instance, women have a different angulation of the hip than men, which resulted in more rapid wearing down of surgical implants\* in women and differences in outcome for pain and mobility.

The changes in FDA policy are intended to bring about better communication of the balance of risk and benefits to the patient and physicians. Awareness of sex, race, and age will help researchers continually identify questions for further study. Finally, evidence has demonstrated that covariates of gender and race/ethnicity (such as size, shape, physiology) should be considered during the design stage of medical devices.

<sup>72</sup> General Accounting Office. "Drugs Withdrawn From Market". (GAO-01-286R). Washington, D.C.: 2001.

\* Birmingham Hip Resurfacing System, manufactured by Smith & Nephew.

<sup>73</sup> Dhruva S. S., et al. Gender Bias in Studies for Food and Drug Administration Premarket Approval of Cardiovascular Devices. *Circulation: Cardiovascular Quality and Outcomes*. 2011 Mar 1; **4**(2):165-71.

<sup>74</sup> Rosamond W., et al. Heart Disease and Stroke Statistics--2007 Update. *Circulation*. 2007 Feb 6; **115**(5):e69-e171.

<sup>75</sup> Shaw L. J., et al. Women and Ischemic Heart Disease: Evolving Knowledge. *J Am Coll Cardiol*. 2009 Oct 20; **54**(17):1561-75.

<sup>76</sup> CDC Division for Heart Disease and Stroke Prevention [Internet]. "Women and Heart Disease Fact Sheet." Atlanta, GA: Centers for Disease Control and Prevention; Copyright 2011. Available from: [http://www.cdc.gov/dhbsp/data\\_statistics/fact\\_sheets/docs/fs\\_women\\_heart.pdf](http://www.cdc.gov/dhbsp/data_statistics/fact_sheets/docs/fs_women_heart.pdf). [Updated: 2011 Dec 20; Accessed: 2011 Nov 9].

<sup>77</sup> Mosca L., et al. National Study of Women's Awareness, Preventive Action, and Barriers to Cardiovascular Health. *Circulation*. 2006 Jan 31; **113**(4):525-34.

<sup>78</sup> Mosca L., et al. National Study of Physician Awareness and Adherence to Cardiovascular Disease Prevention Guidelines. *Circulation*. 2005 Feb 1; **111**(4):499-510.

<sup>79</sup> Chiamonte G. R. and Friend R. Medical students' and residents' gender bias in the diagnosis, treatment, and interpretation of coronary heart disease symptoms. *Health Psychology*. 2006 May; **25**(3):255-66.

<sup>80</sup> Ratliff, N. "Sexes See Stress Differently Before Cardiac Arrest" In American Heart Association's Asian Pacific Scientific Forum. Honolulu, Hawaii. 2002 April 23-26.

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## WOMEN AND MINORITY ENROLLMENT IN NHLBI-SUPPORTED STUDIES

### GENDER DIFFERENCES IN CVD INCIDENCE AND CVD TRIAL ENROLLMENT

Patrice Desvigne-Nickens, MD, presented some of the strides being made by the National Heart, Lung and Blood Institute (NHLBI) in recruiting more women and minorities in clinical trials. The mission of NHLBI is to improve the cardiovascular health of the nation. Cardiovascular disease (CVD) is the primary cause of death for all populations, and differences in CVD often result in the need for specific investigations/analyses with controls. The NHLBI research portfolio includes trials, evaluation of new technology, and diagnostic, monitoring, and development of life-saving procedures.

Despite federal law, NIH, and NHLBI policies, recruiting for clinical trials is especially challenging, as public perception of the drug research industry is not favorable. In a nationwide poll conducted in 2006, less than half of all respondents said they somewhat or very strongly trust the FDA for drug safety, and even less trust the pharmaceutical industry.\*

\* n=1,726 adults interviewed online 2006 Oct 20-30. Available from: <http://www.harrisinteractive.com/news/allnewsbydate.asp?newsid=1216>.

However, NHLBI trial enrollment is diverse. NHLBI-supported research enrolls more women than men, and enrollment of minorities meets or exceeds overall targets. However, women are disproportionately burdened by CVD and overall, CVD trials currently enroll only 22% women.<sup>81</sup> Women are most underrepresented in Phase III trials. Dr. Desvigne-Nickens stated that this might be due to a lack of evidence for sex-specific recommendations in treatment guidelines.

Dr. Desvigne-Nickens outlined two models for sex-based studies in clinical trials. The first is the single sex cohort. Sufficient numbers may be reached, but data may not be generalizable, a feature which can impede marketing. However, these studies are usually successful, and include the Women's Health Initiative (WHI) and Women's Ischemia Syndrome Evaluation (WISE) study. The alternative model includes both sexes with over-sampling. In this event, sex is used as a comparison rather than women as controls. The NHLBI Dynamic Registry and the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack (ALLHAT) are two examples. Dr. Desvigne-Nickens remarked that overall, studies of this type have marginal success.

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#### ENROLLING WOMEN IN TRIALS: CHALLENGES

Two primary challenges in clinical trials are cost and competition. Increases in costs are associated with greater regulatory requirements, human subject safety, and confidentiality concerns. Cost is also affected by increased usage of surrogate endpoints in data analyses, which resulted from decreasing mortality rates and lack of clinical endpoints that directly measure outcome. Competition lies in the choice of enrolling women over men; female participants are associated with greater cost and lower retention. In addition, pregnancy or history of childbirth or hormone treatment may conflict with study criteria. Thus compared to men, women are more likely to be ineligible for clinical trial participation.

Dr. Desvigne-Nickens also identified the IRBs as obstacles to diverse enrollment. Protections around human subject research are necessary, and IRBs play an important role in the process. They give the approval needed to conduct trials and regulations to protect patients, but the process is often lengthy. IRBs should be focused on protecting patients, not blocking research. She says, "IRBs are so often overused and between conflict of interest and focusing on the science it is very hard for these important protections to be done well. They should be focused on the research question, not the details of the design and the specifics of risk benefit." Trial design is already adequately covered by scientific review boards.

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#### ENROLLING WOMEN IN TRIALS: STRATEGIES

NHLBI policy for recruitment of trial participants is to identify outreach methods before initiating enrollment. NHLBI strategies to increase enrollment diversity were similar to other groups: target clinical centers to recruit target population and engage the community in recruitment efforts. One previously unmentioned approach was to pre-determine the number of women needed and maintain open enrollment until all



identified subgroups are completed. A dynamic registry also has the potential to bring in substantial data for observational studies. Dr. Desvigne-Nickens agreed with other speakers on the importance of physicians and investigators. In any trial, the primary endpoint is jeopardized by a lengthy and difficult recruitment process, often making enrollment of women and other subgroups a secondary objective. This must be challenged, and study investigators are critical in this endeavor.

Inclusion of appropriate patient cohorts in cardiovascular trials is essential to improving outcomes. Regulations and policies support appropriate inclusion of women, but the correct strategies for recruiting them must be identified and implemented. Continued improvement in meeting representative cohorts will require effort from sponsors, the research community, and participants. Dr. Desvigne-Nickens said that while there are indisputable barriers to enrolling women, “We must do better.”

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<sup>81</sup> Data presented by P. Desvigne-Nickens in "Dialogues on Diversifying Clinical Trials," Washington, D.C., 2011 Sept 23.  
[http://www.womenshealthresearch.org/site/PageServer?pagename=events\\_clinicaltrials](http://www.womenshealthresearch.org/site/PageServer?pagename=events_clinicaltrials).

## FEDERAL PERSPECTIVES ON CLINICAL RESEARCH REGULATORY INNOVATIONS

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### CHANGING MODELS OF DRUG DEVELOPMENT AND THE ROLE OF REGULATORY SCIENCE

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#### PROBLEMS FACING THE BIOPHARMACEUTICAL INDUSTRY

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FDA strives to give patients access to more innovative products, but there are unique challenges across the landscape. Vicki Seyfert-Margolis, PhD, discussed the problems facing the biopharmaceutical industry today and the current revolution in medicine, which offers a fundamentally different understanding of how to approach disease and drug development.

The biopharmaceutical industry is facing economic difficulties and struggling to meet demands on investments in Research and Development (R&D). Loss of revenue due to patent expirations is a key issue. Dr. Seyfert-Margolis cited that a major pharmaceutical company can lose up to \$100 million revenue when a patent expires – Pfizer is predicted to lose a \$10-billion dollar annual revenue stream following the expiry of its patent on Lipitor® at the end of 2011.<sup>82</sup> Between 2007 and 2010, three dozen drugs lost patent protection. This reality, in combination with declining levels of productivity and innovation, has dealt a major blow to profit margins. While generic medicines make

healthcare more cost-efficient, a lack of revenue sufficient to fund new research projects could dry up the pipeline for new drug development.

### BLOCKBUSTER DRUGS VS. STRATIFIED MEDICINE

What were once known as “blockbuster” drugs are now of the past. Today, 70% of approved drugs do not meet or match their R&D cost.<sup>83</sup> Drug performance in real-world use can be 40-60% lower than the efficacy measured in clinical trials.<sup>84</sup> The risk/benefit profile can shift outside the trial phase when more factors come into play, such as environment, greater patient subpopulations, and drug interactions. Compliance also has a profound impact on drug performance.

Drug developers are now using a model of stratified medicine, a major step towards the ultimate goal of personalized medicine. Stratification is the division of patients into biological subgroups that each require a specific pharmacological intervention;<sup>85</sup> molecular diagnostic testing is used to select the best therapy. Success stories include trastuzumab (Herceptin®) for the treatment of HER2-positive breast cancer, and imatinib (Gleevec®), used in treating chronic myelogenous leukemia. Based on this, drug companies have taken a co-development approach that involves developing a diagnostic and a drug alongside each other. Dr. Seyfert-Margolis revealed that FDA recently approved two novel oncology treatments for lung cancer and melanoma, which were both developed in co-development strategies. The diagnostic test for each was used to screen patients for enrollment in clinical trials. Dr. Seyfert-Margolis believes the parallel development of a drug with its specialized diagnostic is a major advancement that will be critical in future drug research, and could have profound implications for women and minorities. By predetermining the potential suitability of a drug for a specific patient, safety, efficacy, and health outcomes will greatly improve.

In the era of personalized medicine, all drugs will be targeted to not just one disease, but to specific forms of the disease as it manifests in certain populations. In a sense, they will all be “rare diseases” in themselves, requiring their own diagnostics. This, she says, “is a fundamentally different model for how we think about drug development.” Researchers and clinicians will be able to expand on the disease-drug interaction knowledge base to assess the influences of nutrition and other factors to specifically prescribe treatment regimens.

### THE MEDICAL PRODUCT ECOSYSTEM

Dr. Seyfert-Margolis described the medical product arena as an “ecosystem” comprised of multiple players that have traditionally worked in concert in a singular model (Figure 5, page 49). Academia, which is funded primarily by NIH, is considered the discovery engine. Results from these studies in turn direct NIH funding to small companies who conduct additional, often translational, research. Many of these companies are generated from academic research in order to develop a therapeutic from the experimental research. They may be successful in gaining approval through Phase I and Phase II trials, but often lack the capital to fund expensive late-phase studies.

It is at this stage that many of these start-up companies or their product(s) are acquired by major players in the biotechnology or pharmaceutical industry. These large corporations are able to advance the drug through Phase III/IV research. Finally, the drug is marketed to physicians, who are the eventual access point for patients and the public. Private health insurance companies and the government are the main source of revenue for medical products and services, and their willingness to provide or deny coverage influences other aspects of the ecosystem. The changing environment for medical research could lead to a breakdown in this system.

For physicians, a particularly difficult aspect of the advancement of medical science is the “logarithmic” increase in decision-making. Greater variables influencing medical treatments will require more consideration on the part of the doctor to determine the best approach, and he or she will have a wide array of therapies from which to choose. Physicians will have to consider genetic alleles and sub-strata of different types of disease, as well as factor in lifestyle, co-morbidity, sex, race/ethnicity and diet.

#### WHY WE NEED REGULATORY SCIENCE

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Major investments and advances in basic sciences are not fully translating into products to benefit patients. Product development is increasingly costly, success rates remain low, and many uncertainties exist. In addition, the tools and approaches for development and evaluation of medical products have neither kept pace with, nor incorporated, emerging technologies. The economic health of innovative biotechnology and the medical product industry is at risk. Regulatory science is critical in creating a more cost-effective design for drug development. This will continue to be the case while further advances in medicine present challenges to the traditional R&D pipeline and the healthcare economy. As the primary health regulatory agency, FDA is highly invested in regulatory science, which it defines as:

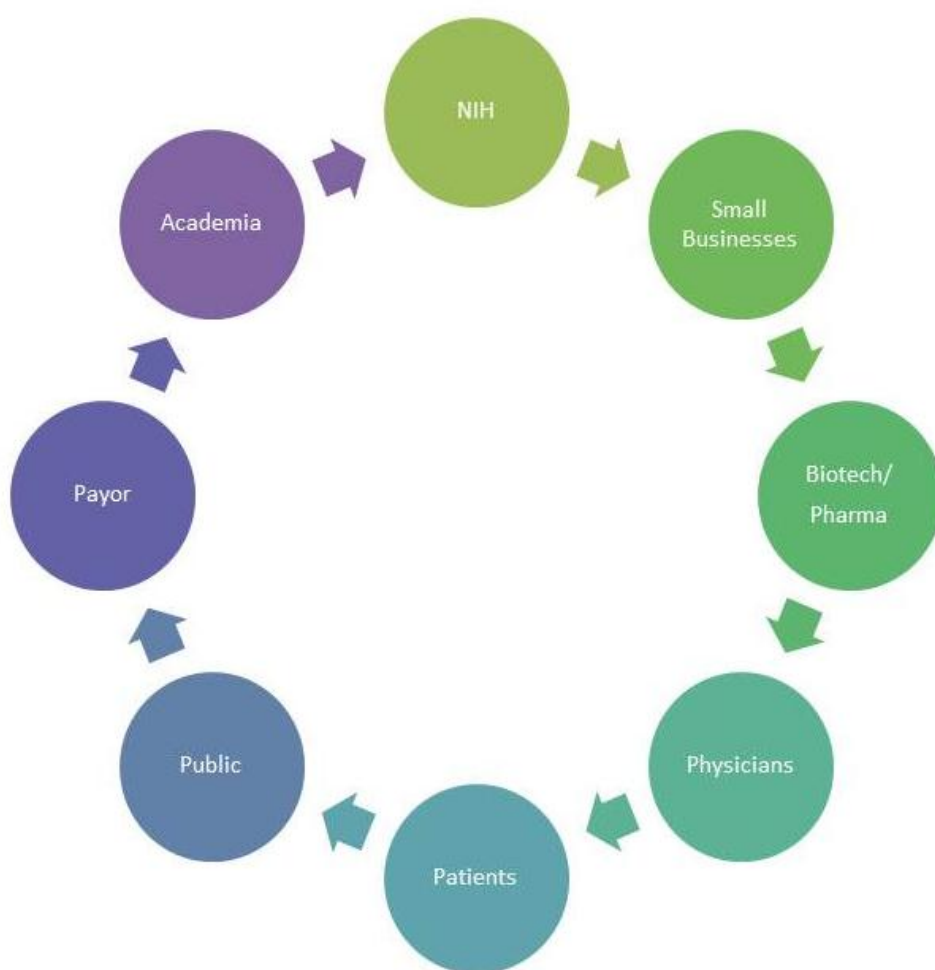
- ◆ The application of basic science to the development and utilization of new tools, standards, and approaches for the assessment of medical product efficacy, safety, and quality;
- ◆ The critical bridge between basic scientific research discoveries and new marketed, medical products.

In August 2011, FDA released its strategic plan “Advancing Regulatory Science at FDA.”<sup>86</sup> Eight priority areas were identified which reflect the agency perspective on what are high priorities for investment in regulatory science.

1. Modernize toxicology to enhance safety
2. Stimulate innovation in clinical evaluation and personalized medicine
3. Support new approaches to improve product manufacturing and quality
4. Ensure FDA readiness to evaluate emerging technologies
5. Harness diverse data through Information Sciences to improve health outcomes
6. Enable a prevention focused food safety system

7. Facilitate development of medical countermeasures to protect U.S. and global health and security
8. Strengthen Social and Behavioral Science to help consumers and professionals make informed decisions

The key implementation components are collaboration and professional development, with an aim to leverage expertise and resources, enhance culture of collaboration, and promote staff scientific training and exchanges. FDA will continue to build partnerships with government agencies and companies in the private sector.



**Figure 5. The Medical Product Ecosystem.** Adapted from presentation by V. Seyfert-Margolis in “Dialogues on Diversifying Clinical Trials,” Washington D.C., 2011 Sept 23.

<sup>82</sup> Willson D. "Drug Firms Face Billions in Losses in '11 as Patents End." *New York Times*, Available from: <http://www.nytimes.com/2011/03/07/business/07drug.html?pagewanted=all>. [Updated: 2011 Mar 6; Accessed: 2012 Jan 11].

<sup>83</sup> Kauffman Foundation. 2008: Assessing Risk and Return: Personalized Medicine Development and New Innovation Paradigm; Available from: [http://www.kauffman.org/uploadedFiles/HHS\\_White\\_Paper\\_1008.pdf](http://www.kauffman.org/uploadedFiles/HHS_White_Paper_1008.pdf). [Accessed: 2011 Nov 8].

<sup>84</sup> *Ibid.*

<sup>85</sup> Jorgensen J. T. A challenging drug development process in the era of personalized medicine. *Drug Discovery Today Special Issue: Pharmacogenetics*. 2011 Oct; **16**(19-20):891-97.

<sup>86</sup> Food and Drug Administration [Internet]. "Advancing Regulatory Science at FDA: A Strategic Plan." Washington, D.C.: U.S. Department of Health and Human Services, Food and Drug Administration; Copyright 2011. Available from: <http://www.fda.gov/downloads/ScienceResearch/SpecialTopics/RegulatoryScience/UCM268225.pdf>. [Updated: 2011 Nov 9; Accessed: 2011 Nov 9].

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## PERSPECTIVES ON CLINICAL REGULATORY RESEARCH INNOVATIONS

### FAILURES AND CHALLENGES IN CLINICAL RESEARCH

Garry Neil, MD, began his talk by describing the unique nature of the healthcare system. It involves everyone in the world – we are all patients – and we are the subjects of our inquiries and the beneficiaries who will gain from research advances, either directly or indirectly. All the elements of the enterprise – companies, individuals, providers, regulators, industry, government funders, and consumers – have a big stake in the outcome. He echoed Dr. Seyfert-Margolis' sentiments about healthcare as an ecosystem. Dr. Neil said, "If we're not doing well – the ecosystem isn't really healthy – it's not contributing what it needs to, and we are going to see perturbations in healthcare delivery . . . and cost."

Dr. Neil believes the current shortcomings lie particularly in drug development. Most of the \$100 billion spent on research yearly goes to Phase III trials, but about 50% of these end in failure. Between 2007 and 2010, eighty-three drugs failed in Phase III trials.<sup>87</sup> Efficacy and safety issues accounted for 90% failures across all therapeutic areas (Figure 6, page 51).

What is holding us back? Understanding biology and the targets are the keys to success. Dr. Neil explained that drug development success (better treatment effect) is directly related to the level of knowledge of the mechanism (Figure 7, page 52). Low comprehension is reflected in poor treatment effect.

Dr. Neil also discussed the importance of translational medicine and biomarkers in biopharmaceutical research. Research from *in vitro* models or animal studies must be translated to understand what is happening to humans, but this can be difficult to extrapolate. This meeting has already presented gender- and race/ethnicity-related variations, but there are many other factors, including age, genetic background, dietary behaviors, environment, and cultural influences. Dr. Neil said, "The challenging thing is...people are different. Even though we have so much in common, those individual

differences are really, really important.” Most importantly, those differences need to be understood early on in drug development.

### BUILDING A NATIONAL CLINICAL TRIALS INFRASTRUCTURE

A robust clinical trials infrastructure is necessary for success, and the current industry practice is to create that infrastructure *de novo* with each study, a practice that is both inefficient and expensive. This is further compounded by the barriers to enrollment, which are known to be even more problematic for women and minority groups.

Dr. Neil recognizes there is work to be done to improve the status quo, and he advocates for the building of a clinical trials infrastructure on a national level. He was positive about the initiatives being implemented by FDA, and said that public-private partnerships will be necessary, as industry cannot build a clinical trials infrastructure on its own. One question is how to raise Safety Monitoring Boards (SMBs) or IRBs to a national or regional level. Standardization of protocols and data collection is a requisite, but even more pressing is the need for investigators. There is a small pool of trained PIs in the U.S. and as a result, only 3% of all eligible patients ultimately enroll in a study. All parties must work together to build awareness, such that ultimately, target populations are reflected in clinical trial populations.

- Not disclosed
- Financial and/or commercial
- Safety
- Efficacy



**Figure 6. Reasons for Phase III Clinical Trial Failures. Adapted from Arrowsmith et al., 2011.<sup>87</sup>**

### NEW TOOLS FOR BETTER RESEARCH

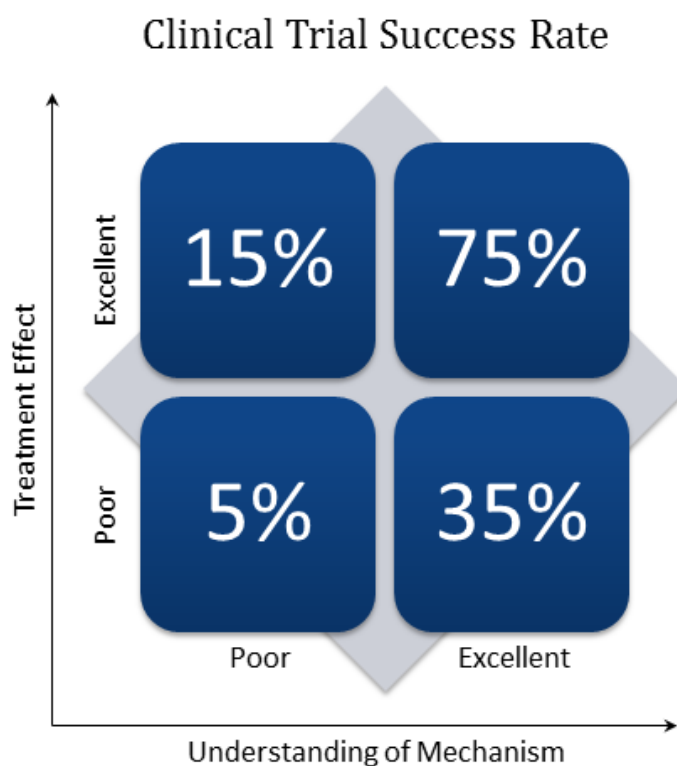
Johnson & Johnson (J&J) has developed data sharing consortia and tools to better understand biology. TranSMART (Translational Medicine Mart) began as a software tool and database built for J&J’s own internal use, but they are now making it available in open-source format and working with partners to expand the network.<sup>88</sup>

Dr. Neil introduced the innovative approach of Direct-to-Participant (D2P) Trials. This model centers around one “site” which conducts trials with participants throughout the U.S. Patients and investigators are linked by web, phone, and wireless technologies. The benefits of D2P trials are two-fold: reduced cost by eliminating “bricks-and-mortar” sites, which account for approximately 75% of the cost of clinical trials, and increased enrollment from outreach to more participants. Only a small fraction of eligible subjects lives within reach of centers. In a D2P trial, home tests and study drugs can be delivered directly to the participant. Mytrus, Inc. is already using the D2P method to bring clinical trials into patients’ homes.

Dr. Neil reinforced the need for minority patient and physician recruitment efforts based on U.S. ethnic demographics. Between 2010 and 2050, White non-Hispanics will drop to just 46.3% of the total U.S. population. In 2040, California, New Mexico, and Texas are all expected to have over 50% minority population, as are four of the top-five largest cities in the

U.S. J&J has taken on the challenge to identify potential new investigators from minority groups. They are working with the National Hispanic Medical Association, National Medical Association, American Association of Physicians of Indian Origin, National Minority Quality Forum, and the Society for Women’s Health Research to identify experienced investigators. They are identifying and resolving barriers to recruiting women and minorities, and as of

2010, over one-third of J&J's clinical trial participants are non-White,<sup>\*</sup> and over half of all participants are female.<sup>†,89</sup> Their trial populations are thus much closer to reflecting the U.S. population.



**Figure 7. Drug development success stems from an understanding of the biological mechanisms of the product and the target. Adapted by G. Neil based on work by E. Zerhouni**

<sup>87</sup> Arrowsmith J. Trial watch: Phase III and submission failures: 2007-2010. *Nat Rev Drug Discov*. 2011 Feb; **10**(2):87.

<sup>88</sup> *Bio-IT World* [Internet]. "Running transSMART for the Drug Development Marathon." Needham, MA: Cambridge Bio Collaborative Inc.; Copyright 2002-2011. Available from: <http://www.bio-itworld.com/issues/2010/jan/transmart.html>. [Updated: 2011 Jan 12; Accessed: 2011 Jan 12].

<sup>89</sup> Data from Johnson & Johnson Global Clinical Operations, presented by G. Neil in "Dialogues on Diversifying Clinical Trials," Washington, D.C., 2011 Sept 23. [http://www.womenshealthresearch.org/site/PageServer?pagename=events\\_clinicaltrials](http://www.womenshealthresearch.org/site/PageServer?pagename=events_clinicaltrials).

<sup>\*</sup> n=19,338 subjects, U.S. trials only.

<sup>†</sup> n=57,553 subjects, U.S. trials only

## CONCLUSION

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In the “Dialogues on Diversifying Clinical Trials,” meeting, leading experts from industry, academia, and regulatory bodies presented data on women and ethnic/racial minority representation in clinical trials, past and present, as well as emerging trends in technology and regulation and successful strategies for increasing trial population diversity.

Historically minorities are underrepresented in clinical trials, especially with regard to cancer research, HIV/AIDS, women’s health and psychiatric research. Over the last several decades substantial improvements have been made in response to new legislation and regulatory guidelines, however the fact remains that females and racial and ethnic minorities are not included in medical research in adequate numbers.

Women use the healthcare system more than men do,<sup>90</sup> and the changing demographics of the U.S. population mean that minority consumers in healthcare will eventually be a majority. Without adequate representation of women and minorities in clinical trials, important side effects or negative outcomes may not be discovered. Dr. Jose Reynal of the PhRMA Diversity Committee said, “We may see data in Phase IV that may raise safety and/or efficacy concerns.”

Studies show that a large majority of Americans believe in the importance of clinical trial research. Speakers from the meeting provided evidence that this positive outlook includes women and minorities. However, in a nationally representative survey of over 7,000 Americans, African-American and Asians were significantly less likely to have heard of clinical trials compared to Whites.<sup>91</sup> Several examples were presented where enrollment was increased through campaigns to improve disease awareness and advertise clinical trials. While the different sessions in “Dialogues on Diversifying Clinical Trials” varied in their approach, they all stressed the need for transparency on the part of investigators to gain trust from study participants.

Studies have shown that the most effective means for recruiting patients to clinical trials is through physician referral.<sup>92</sup> For this reason, a number of speakers at the meeting stressed the need to recruit female and minority physicians. There are some barriers to this, but better investigator training and emphasis on the rewards of clinical trial research will help to set this straight.

The meeting also highlighted the role of regulatory agencies and review bodies in maintaining and promoting adequate standards for trial design. One critical aspect in regulation is the need for components that facilitate, rather than hinder, medical research. The unnecessary burden placed on trial sponsors can be felt both logistically and financially; stringent inclusion requirements make diverse patient enrollment more difficult, which then requires greater spending on recruitment efforts. A clear message from the “Dialogues on Diversifying Clinical Trials” conference was the desire to



implement new and emerging technology to enable better inclusion of women and minorities. A wide array of advocacy groups and networks is implementing novel strategies to recruit, support, and retain both patients and physicians from diverse backgrounds to improve trial design and outcome.

To summarize the major findings of the meeting:

- ◆ Women and minority patients and physicians are willing and necessary participants in medical research.
- ◆ Trust, communication, education, and building a presence within the community are successful means to increasing diversity in clinical trials.
- ◆ Collaborative efforts are essential across all sectors of medical product research and development.
- ◆ Regulatory and review bodies must focus on patients' needs and facilitate the clinical trial process.

Clinical trial diversity is an issue that goes far beyond improved efficacy and medical safety. At its core, diverse enrollment represents social justice. Speaking at the conference, Carlton Haywood Jr., MD, PhD, of the Johns Hopkins Berman Institute of Bioethics said, "at the end of the day, [inclusion of women and minorities in clinical trial research] is the right thing to do."

There is much to consider in diversifying clinical trial enrollment, but the outlook is promising. The changing face of medical product research and development and technological advancement, coupled with a rapidly evolving population, means exciting times are ahead. The entire field will have to anticipate change and adapt accordingly. Access to clinical trials can mean the difference between life and death, and equal access to healthcare and quality of treatment will benefit all. Ultimately, there are no more excuses to conduct trials without statistically meaningful numbers of subgroup participants.

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<sup>90</sup> Bertakis K. D., et al. Gender Differences in the Utilization of Health Care Services. *J Fam Pract.* 2000; **49**(2):147-52.

<sup>91</sup> Brown M. and Moyer A. Predictors of awareness of clinical trials and feelings about the use of medical information for research in a nationally representative US sample. *Ethnicity & Health.* 2010; **15**(3):223-36.

<sup>92</sup> Hudson S. V., et al. Physician perspectives on cancer clinical trials and barriers to minority recruitment. *Cancer Control.* 2005; **12**(Suppl 2):93-6.

## SPECIAL INTEREST SESSIONS

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Participants were given the opportunity to meet in special interest sessions led by subject experts. By facilitating discussion on specialized topics within small groups, the organizers hoped to glean new insights into successful strategies for the improvement of clinical trials research. Each conference participant was able to attend three different brainstorming sessions of approximately 35 minutes each. The three questions posed to the participants were:

1. What was innovative about the approach discussed by the lead?
2. Can this approach be widely used to enhance clinical trial design? Research data and outcomes? How?
3. How will this approach improve recruitment and retention of women and minorities in clinical trials?
4. Other comments

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### WITHIN3 ONLINE COMMUNITY

Jim Bennett is a member of the Board of Directors of Within3, a social networking provider that creates and cultivates online communities for engaging professionals in pharmaceuticals, medical associations and health systems. An online two-way community – either for a single trial or as an ongoing Investigator Portal/Community – is an innovative tool that can greatly enhance collaboration and communication in a complex, dispersed trial. With dozens of features and functions, such a community complements existing Clinical Trial Management System (CTMS) and support systems by streamlining work and reducing time spent in ramp up and close-down, study initiation, patient recruiting, and ongoing trial management. In his discussion, Bennett described online communities, illustrated how they work, and explained why they are being rapidly adopted.

1. The innovative characteristics of Within3 are its comprehensiveness, security, and specific focus on the unique needs of health professionals.
2. Regarding the potential for Within3 to enhance trial design or research data and outcomes, responses from the discussion participants were mixed. A major positive aspect identified was the potential to maintain discussion and collaboration among investigators while reducing the time and expense of travel to meetings, and it allows for “constant interaction” among network members. In theory, it should be widely applicable to many types of trials.
3. Many were not sure that it could improve recruitment or retention of women and minorities in clinical trials; however, it was noted that it could improve awareness or facilitate dialogue among investigators.
4. Within3 is a “very interesting, intriguing tool.”

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### RAISING MINORITY RECRUITMENT AWARENESS

Karen Brooks is Senior Director of Project Delivery at PRA International, a global CRO specializing in oncology, central nervous system, respiratory/allergy, cardiovascular, and infectious diseases. Brooks presented new and successful ways to improve minority recruitment in clinical trials.

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The discussion included potential regulatory implications to minority recruitment, ideas for raising awareness within an organization, and innovative ways to support investigator sites in minority recruitment.

1. She emphasized the importance of linking regional medical liaisons and Clinical Research Associates (CRAs) together, and training CRAs to target places of high minority incidence (churches, historically Black colleges), for recruitment. She explained the usefulness of providing investigators with a “tool kit” of resources and brochures designed specifically for the targeted minority population, in order to raise awareness of the importance of clinical trials. She provided an interesting idea for pushing for more trial sites: linking CRA bonuses with a requirement to nurture at least two “naïve” sites per year.
2. The approach is straightforward and basic enough to be used by a wide variety of organizations. First, team awareness of the importance of minorities in clinical trials must be raised. Project managers must be invested in the goal. Next, the team of investigators must be trained on how to best reach and involve minorities (they are provided with perspectives on the targeted minority’s health care experiences, brochures and materials to distribute, etc.). Finally, CRAs and investigators raise community awareness on clinical trial importance with the use of materials provided by the Center for Information and Study on Clinical Research Participation (CISCRP) and Project IMPACT (Increase Minority Participation and Awareness of Clinical Trials). This enhances clinical trial design and research outcome by improving involvement of all involved in a clinical trial.
3. Recruitment is enhanced due to better targeting of places with high minority incidence and improved community understanding of clinical trials (that may lead to more willingness to participate). Retention can be improved through texting/cell phone updates.

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#### PATIENT ACCESS TO TRIALS AND POSSIBLE DATA ANALYSES

Wendy Carter, DO, is a Medical Officer at FDA’s Center for Drug Evaluation and Research, Division of Antiviral Products (DAVP) in Silver Spring, Maryland. Dr. Carter discussed FDA’s role in promoting efforts towards enrollment of women and minorities in clinical trials and DAVP’s experiences with recruitment efforts for women and minorities into clinical trials. She described how DAVP communicates with sponsors and advocacy groups to promote enrollment of women and minorities into clinical trials, and how FDA and DAVP evaluate data with regard to women and minorities during the review process.

1. The innovative approach is to communicate with sponsors, with a focus on recruitment efforts for women and minorities.
  2. The approach could be used to enhance clinical trial design by promoting equitable representation of women and minorities.
  3. The approach could improve recruitment and retention by inviting advocates and sponsors to discuss strategies, successes and failures with others to fully comprehend the challenges faced in recruiting women and minorities.
  4. Phase III trials are not powered to assess trends in subgroups. In order to make an impact, analysis should be done in Phase III, not just postmarketing studies.
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### INSTITUTIONAL REVIEW BOARD (IRB) CHALLENGES AND SOLUTIONS

Jennifer Chadwick, BS, is the Native American Programs Coordinator at the University of Oklahoma Health Sciences Center. She develops and maintains essential relationships with Native American partners in the Treatment Options for Type 2 Diabetes in Adolescents and Youth (TODAY) Study, and has worked with families and tribal programs for over ten years. In her discussion, Chadwick illustrated the process of creating and implementing an effective collaboration between a national clinical trial (TODAY Study) and multiple tribal health and American Indian (AI) IRBs. She described the University of Oklahoma Health Science Center and AI/tribal health partnerships before the TODAY Study. She then went on to explain the steps in developing a collaborative partnership between tribes, universities, and/or national clinical trials, and the possible AI/tribal IRB concerns and how these might be different from a university IRB. The TODAY Study experience is an example of how AI IRBs might compromise in an effort to partner. Chadwick discussed the formation and function of the TODAY Study Native American Publications Sub-Committee, and explained how the Sub-Committee design lends itself to additional collaborative research opportunities.

1. Pediatric endocrinology services were provided by Dr. Kenneth Copeland, who hired a Native American Coordinator. The Choctaw Nation is putting aside \$2500/tribal member annually to use toward health related care.
2. This approach cannot be widely used to enhance clinical trial design, research data and outcomes because it is too specific to the Native American population.
3. This approach will not improve recruitment and retention of women and minorities in clinical trials, outside the targeted Native American communities.
4. This is a reasonable innovation but risky - bad protocols may still be implemented without careful oversight by the University of Oklahoma. "Excellent efforts but the system is broken." There were differences in pediatric patients of Native American population; the pediatricians were not collecting height and weight data on kids, making it harder to identify pediatric diabetes early. There is a correlation between the prevalence of casinos/wealth and diet, increasing presence of certain disease states.

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### SISTER TALK HARTFORD STUDY AND RESULTS

Judith Fifield, PhD, is the Director for the Ethel Donaghue Center for Translating Research into Practice and Policy at the University of Connecticut Health Center (TRIPP Center), and Principal Investigator on the SisterTalk Hartford study. The study was informed by a theory that focuses on the context, motivations, expectations and unique social, cultural, and economic circumstances of the target population. They utilized a community-based participatory research approach to a randomized, controlled, church-based trial and translated the principles of achieving a healthy lifestyle into faith-based and church-placed programming. SisterTalk was a successful study, with high retention rates and significant improvement in BMI through changes in fat intake.

1. SisterTalk was innovative in its faith-based approach; the use of the church community is an ideal site to recruit potential clinical trial participants. Most churches now have web sites, and there is an elaborate health ministry structure. There are practical benefits of health to the congregation, such
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- as weight loss, healthy eating, and reducing asthma and diabetes. Black churches are a particularly energizing model with diverse ministries and incredible infrastructure.
2. The approach can be used to enhance trial design because people go to church more often than they see their physician. Their church is a “safe zone” where trust is already established, and one of the most effective ways to reach the African-American community. National church leadership would need to be encouraged to work with the pharmaceutical industry. This method can improve results through the sharing of abstracts and papers with a CAB.
  3. This approach can increase inclusion and access, and facilitate transportation to and from the site, since it is a place they would normally go to once a week. Mega-churches can reach more African-American women in one visit than in almost any other setting. Testimonies from members encourages enrollment, and the church body acts as a support network to increase adherence to the program. Development of a research network across churches is another possibility. A CAB reviews all materials and language to ensure the message is communicated most effectively. The pastor’s wife can be viewed as a trusted leader, and church members will listen to her more than an outsider, which will improve both recruitment and retention. By making the program a type of community service effort, participants gain satisfaction and are invested in the program, improving retention.
  4. Because each church is unique, the program was a hybrid. The resource center is viewed as the “mothership” which finds new churches, updates materials and is the foundation of the clinical trial. They will distribute a “plug and play” box with video and all the necessary programs. A second model is to make churches more independent and able to self-sustain the trial, however, some churches may lack the infrastructure to maintain it. The next phase will include a reward/incentive system to further motivate participants and increase retention. Essentially the mission is to make connections regarding the use of the word “patient” versus “subject/consumer.” A two-year study on diabetes will include faith-based interaction post efforts.

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## CMS COVERAGE

Rosemarie Hakim, PhD, is a Senior Research Advisor at the Centers for Medicare and Medicaid Services (CMS). James Rollins, MD, is Director of the Division of Items and Devices within the Coverage and Analysis Group at the Office of Clinical Standards and Quality at CMS. Medicare and Medicaid offer people with Medicare and Medicaid the option to join some clinical trials for the diagnosis and treatment of illnesses by paying some of the patient costs.<sup>93</sup> There are three vehicles to cover clinical trial care: Coverage with Evidence Development (CED) program, Clinical Trial Policy (CTP), and Investigational Device Exemption (IDE). Hakim and Rollins discussed how and why CMS makes coverage decisions, and the evidence required.

1. Existing policies that can be at odds with each other create a disincentive for conducting clinical trials for underserved populations, including elderly and minorities on Medicare and Medicaid. This is particularly true in industry, where elderly participation is avoided. CMS is addressing this issue to create policies that allow for reimbursement of costs in a clinical trial.<sup>94</sup> For instance, CMS can pay for bed-days for in-hospital studies that require hospital stays. CTP requires justification for excluding minorities, CED specifically.
  2. This approach should be widely applicable, as it is not specifically oriented toward any particular type
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of study. However, it is particularly important for clinical trials investigating diseases that disproportionately affect the elderly or minorities. It will enhance trial design, data collection, and outcomes by diversifying the study population.

3. It is not necessarily a means to draw in more participants, but rather makes the option feasible. Investigators and sponsors still need concerted efforts to make potential study participants aware of clinical trials. However, there are no stats on whether or not the elderly have been included in trials. Information was not provided if CMS policies have had an impact on recruitment and retention of women and minorities.
4. Is there a requirement to report which services are utilized under CMS during clinical trials? The issue is unclear. One example given of a problem was the Wingspan Stent System, which, when ineffective in preventing incidence of stroke or death, was not covered by Medicare. Bottom line: there are policies that are at cross-purposes to industry-sponsored clinical trials and result in exclusion of underserved populations that otherwise use CMS services.

Clinical trials that are deemed to qualify automatically are: \*

- ◆ Trials funded by NIH, CDC, AHRQ, CMS, DOD, and VA;
- ◆ Trials supported by centers or cooperative groups that are funded by NIH, CDC, AHRQ, CMS, DOD, and VA;
- ◆ Trials conducted under an Investigational New Drug (IND) Application reviewed by FDA; and
- ◆ Drug trials that are exempt from having an IND under 21 CFR 312.2(b)(1) will be deemed automatically qualified until the qualifying criteria are developed and the certification process is in place. At that time, the Principal Investigators of these trials must certify that the trials meet the qualifying criteria in order to maintain Medicare coverage of routine costs. This certification process will only affect the future status of the trial, and will not be used retroactively

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<sup>93</sup> U.S. Department of Health and Human Services, Health Care Financing Administration. "Medicare and Clinical Trials". (HCFA-02226). Baltimore, MD: 2001.

<sup>94</sup> *Centers for Medicare and Medicaid Services* [Internet]. "Medicare Clinical Trial Policies." Baltimore, Maryland: U.S. Department of Health & Human Services; Copyright 2011. Available from: <https://www.cms.gov/ClinicalTrialPolicies/>. [Updated: 2011 Jun 29; Accessed: 2011 Oct 26].

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\* For more information, visit <https://www.cms.gov/clinicalTrialPolicies/Downloads/finalNationalcoverage.pdf>.

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## INVESTIGATOR/TEAM DYNAMICS

E. Francis Jones is President and CEO of Innovative Clinical Concepts, LLC (ICC), a clinical trial research service organization that provides specialized services to study sponsors/CROs, with a focus on physicians and clinical practices who serve minority, underrepresented, and women patient populations. ICC's mission is to provide high quality, efficient and ethical clinical trial support services. Jones discussed investigator/team dynamics, specifically: including the investigator as part of the research team; developing long-term relationships with investigators; the roles an investigator can play within a research team.

1. The innovative approach of ICC is the providing of community-based clinical trial investigators, who, through their community participation, directly increase enrollment of underrepresented minority populations (African-Americans, Latinos and Asians, etc.). ICC provides a subject matter expert (SME) to consult during protocol development. Industry generally approaches key opinion leaders (KOLs) as national coordinators, and KOLs are often removed from patient care. ICC provides training to the PI early on (6 hours face-to-face training, followed up through the cycle of the study). The PI is also included on the Advisory Board.
2. ICC's approach could be widely implemented to enhance trial design, and through more effective and diverse recruitment, their efforts should improve data collection and outcomes.
3. It was generally agreed that ICC's methods would improve recruitment of women and minorities. ICC helps to build infrastructure for the trial and provides incentive, both of which will increase recruitment and retention. ICC focuses on the enrollment of women and minorities to improve recruitment of these groups, however it is not fully clear if their methods will improve retention. Most PIs and research staff treat clinic patients and research patients the same, when they are not - study participants will have different needs.

It was noted that ICC's methods are similar to those of Covance, the important part being that they train and then "release" the site for autonomy. ICC recruits investigators early in their careers, and younger minority investigators seem to have access to more minority patients. Sponsor support can help new minority investigators. There should be a "menu" of incentives, not just co-authorship on publications. Academics want to publish, but what other incentives can be provided? Ultimately, minority investigators are still in business to make money. Throughout the discussion, it was not mentioned if there are different methods to train community-based physicians as opposed to those carrying out studies in hospitals or large institutions. The environment fostered by ICC is meant to give study coordinators greater and more principal roles in clinical trials, and increase communication between investigators and sponsors, and investigators with site staff. The PI should have an open relationship with the IRB and the IRB should more closely oversee the PI. At the same time, the PI should not over-delegate tasks to staff. Essentially the aim is to re-examine the role of the investigator in the research process, however the question remained if this raised regulatory concerns.

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## EVALUATION OF GENDER EFFECT IN NEW DRUG APPLICATION (NDA) AT FDA

Joo-Yeon Lee, PhD is a Senior Reviewer in the Division of Pharmacometrics in the Office of Clinical Pharmacology, Office of Translational Science, CDER, FDA. Dr. Lee discussed a covariate analysis to identify gender difference in pharmacokinetics and analysis of subgroup populations for efficacy and safety of drugs.

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1. In a drug trial, investigators revealed a relationship between QTc\* and drug concentration, which differed between Caucasian and Asian populations. They hypothesized that: (1) Females had higher drug concentrations than males; (2) Female shows more sensitivity impact on dosing, which puts that at higher risk for cardiac event. Investigators were able to differentiate the risk factor for QTc based on that data.
2. The approach could have an impact on late trial studies. The study revealed that trial design should take into account differences between men and women, and this must be differentiated on the label.
3. The approach will improve recruitment and retention of women and minorities through closer monitoring of results and reduction of negative events.
4. Females are at higher risk for QTc event. How do we address conclusions of more minorities in trials?

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## DATA STANDARDS

Jonathan Levine, PhD, is a Senior Scientific Policy Analyst in the Office of the Commissioner at FDA.

Before one can choose standards, the following questions need to be addressed:

- ◆ How will the data be used, exchanged?
  - ◆ What information model should be used?
  - ◆ What content needs to be exchanged?
  - ◆ What terminologies will be used?
  - ◆ What types of datasets will users of the data need?
  - ◆ How can you collect the data with a minimum number of errors?
1. Electronic health records vary across organizations, agencies, and countries. For instance, sex could be coded as “male” or “female”; “M” or “F”; “0” or “1”; “1” or “2”. Current coding standards for sex advocate use of “M,” “F,” and “U,” to represent male, female, or unknown, respectively. A code must represent the written in the adverse event description and results should go directly to a data collector. Health Level 7 (HL7) is an international community of healthcare subject matter experts and information scientists collaborating to create standards for the exchange, management and integration of electronic healthcare information; they promote the use of such informatics.<sup>†</sup>
  2. How the data will be used is not necessarily a problem at hand; data is used for evaluation of efficacy and safety. Automatic collection is better than manual entry and improves trial design and analysis. HL7 also facilitates data exchange across PCs and software programs. It is also useful for regulatory agencies. Small-area analysis uncovers local-level disparities often masked by health estimate for large areas (cities, counties, states). Drug safety information can be gleaned from relating small-area estimation from case report forms.
  3. Informatics standards within and among healthcare organizations will increase the effectiveness and efficiency of healthcare information delivery for the benefit of all. This approach could enhance

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\* The QT interval is a measure of the time between the start of the Q wave and the end of the T wave in the heart’s electrical cycle. A prolonged QT interval is a biomarker for ventricular tachyarrhythmias and a risk for sudden death. QTc is the QT interval corrected for heart rate.

<sup>†</sup> HL7 and its members provide a framework (and related standards) for the exchange, integration, sharing, and retrieval of electronic health information. They standardize coding for information such as gender and medical terminologies. “HL7” is also used to refer to some of the specific standards created by the organization.



design and outcome by allowing for better comparison across studies. There must be deep insight of data collection method (frequency, format, instruction to the sites and patients) to achieve the real goal/endpoint of the trial.

4. Trying to harmonize coding might end in bias, but it is necessary to analyze the data. Coding must also represent narrative. For example, “woke up due to asthma attack” can be coded as “sleep disorder”. Going to one entry will avoid human error.

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## COMMUNICATION AND EDUCATION: A KEY TOOL TO MINORITY RECRUITMENT

Beverly Lyn-Cook, PhD, is a Senior Scientist at FDA. Her research interests include nutrigenomics, pharmacogenomics, epigenomics and chemoprevention of cancer. She is particularly interested in the link between diet, hormones and cancer development and ethnic disparities in breast cancer. In her discussion, Dr. Lyn-Cook addressed aspects of communication and education in minority recruitment.

1. Two approaches for community outreach to patients:

### Communication:

- ◆ Patient characteristics and disease prevalence to target populations
- ◆ Use interpreter for illiteracy and lack of English proficiency
- ◆ Target population cultural values/customs (social, economic and educationally disadvantaged)
- ◆ Use gatekeepers in the target community – must have confidence in the project leaders
- ◆ Continue communication through newsletters, health fairs, study outcomes, churches, and barbershops
- ◆ Establish a research day with target community for feedback questions and answers about the particular study and its role in the disease

### Education:

- ◆ Educate about how the participants will be compensated, without coercion or undue influence
  - ◆ Assure confidentiality
  - ◆ Educate target population in lay terminology about the importance of adequate minority participation in clinical trials and the consent process
  - ◆ Use audio or other culturally-specific education strategies with target population
  - ◆ Educate on health behaviors and importance of adhering to prescribed regimens
2. This approach can be widely used to enhance trial design. It started the dialogue that sponsors should consider patient outreach early and as an integral part of every research project.
  3. It will increase minority participation – if done correctly – since it brings about community and patient awareness.

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## INCREASING MINORITY ACCRUAL TO CANCER CLINICAL TRIALS: WHAT WILL IT TAKE? NEW PERSPECTIVES ON EDUCATION AND ADVOCACY FOR THE PUBLIC, PATIENTS, RESEARCHERS, AND COMMUNITY HEALTH PROVIDERS

Margo Michaels, MPH, is Founder, Executive Director and President of the Education Network to Advance Cancer Clinical Trials (ENACCT). She is considered a national expert in community-based education efforts around cancer clinical research. Participation in cancer treatment clinical trials (CCTs) is a key measure for delivery of quality cancer care.<sup>95</sup> Nonetheless, only 3% of patients participate, with even fewer from minority and medically underserved groups.<sup>96</sup> While numerous challenges face the cancer clinical research system, there are several well-documented barriers to CCT participation that ENACCT has effectively addressed through cross-sector collaborative education and advocacy efforts.<sup>97</sup>

1. Community approach to enhancing clinical trial literacy included simultaneous engagement of three key audiences, with messages tailored to their respective roles in influencing decisions about clinical trial participation. The three groups identified within the discussion were community leaders (ambassadors for social justice); primary care providers (cracking the door for subsequent trial discussions), and research teams (enhancing cultural competency).
2. Success measure – inquiries about rather than accrual to trials – appropriately reflects what community audiences can influence. The approach resulted in significant increases in both phone and web inquiries about trials. This model of community engagement is replicable in a variety of communities. However, there are impediments to its broad use, including: primary care providers do not know where trials are taking place, and availability of trials does not drive referrals; patients need insurance to be able to afford clinical trial participation; clinical trials are still viewed as a last resort, when no other options exist. The community-based approach must be culturally sensitive, recognizing significant differences among populations with respect to what is relevant: African-Americans (trust); Latinos (quality of care and concerns about deportation); and Asians (concerns about receiving substandard care).
3. The approach recognizes the key role of those in a position to refer/recommend patients for trials. The model could help address cultural bias in trial referral and enhance trust by leveraging existing relationships with primary care and community leaders – greater trust leads to better recruitment and retention.
4. There is a need to ensure understanding of the term “standard of care” to put investigational therapy in trial in context. One must recognize that the word “drug” is not monolithic and may be equated with addiction in some communities. Depending on the ethnic minority community, they may think of different issues. Concern about “kickbacks” limits the ability of industry to provide infrastructure and supplies needed to maintain trials in the community. Peer-to-peer networking can facilitate referrals to trials.

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<sup>95</sup> The American College of Surgeons, Commission on Cancer Standards. "Cancer Program Standards". Chicago, IL: The American College of Surgeons; 2009. Available from: <http://www.facs.org/cancer/coc/cocprogramstandards.pdf>. [Accessed: 2011 Nov 7].

<sup>96</sup> Murthy V. H. and Krumholz H. M. Participation in cancer clinical trials: race-, sex-, and age-based disparities. *JAMA*. 2004; **291**(22):2720-6.

<sup>97</sup> Michaels M., et al. The Promise of Community-Based Advocacy and Education Efforts for Increasing Cancer Clinical Trials Accrual. *J Canc Educ*. 2011:1-8.

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## MODERN TECHNOLOGY AND CLINICAL TRIALS

Mark Plaskow, Chief Technology Officer, and Steve Barns, Chief Legal Officer, at American Health Technology (AHT) presented the Ohio-based company's product, which provides a novel automated analysis framework for diagnostics and toxicology. Their technology is being implemented for specific software applications for drug development in oncology, hematology, diabetes, parasitemia, and in veterinary practice.

Capabilities of modern technology for enhanced demographic data for women and minority representation in clinical trials were discussed. Automated, exact, standardized and quantified study data of compound effects on the endocrine system during Stage I will replace the current subjectivity and high variation with "1 to 4" (minimal, mild, moderate, marked) evaluation. These capabilities also allow pharmaceutical developers to quantify the effect of environmental Bisphenol A (BPAs) by sex, ethnicity, and other demographical classifications. More efficient R&D and superior data for FDA submissions will result.

1. AHT's product provides highly increased resolution of the effects of drugs on cells, with the potential for visualizing metastatic cells. AHT also shows increased improvement in measuring endocrine dysfunction. What a pathologist can do in 5.0 seconds, their automated microscopy can do in 0.5 seconds. The AHT Malaria Pathology Assistant uses single blood-stick collection technology. It has been used on samples from African children to test for malaria. AHT could have a huge impact on global health.
2. The approach could be widely used to enhance trial design because it dramatically cuts time and labor for pathologists in data collection, and a much larger sample size can be considered. AHT could have a positive impact on research data and outcomes because pre-clinically it can screen out drug candidates more quickly by demonstrating proof of a drug's effect on glands and cells in rats. By exactly quantifying dose-response and toxicological data, it can provide researchers with better data from which to make their conclusions about drug safety and efficacy.
3. The approach generally will not improve recruitment and retention of women and minorities to clinical trials, however it does facilitate analysis of a greater number of specimens across the globe, which will include a more diverse sample set.
4. An estimated 216 million people were infected with malaria in 2010,<sup>98</sup> and enhanced diagnostic testing could have a great impact on global health. Viruses are too small to be analyzed by AHT software, but there is potential for other blood-borne pathogens, such as tuberculosis and leishmaniasis. It is useful for analyzing fecal parasites in a veterinary setting.

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<sup>98</sup> World Health Organization. "World Malaria Report: 2011". Geneva, Switzerland: World Health Organization; 2011. Available from: [http://www.who.int/malaria/world\\_malaria\\_report\\_2011/9789241564403\\_eng.pdf](http://www.who.int/malaria/world_malaria_report_2011/9789241564403_eng.pdf). [Accessed: 2012 Jan 13].

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## INVESTIGATOR-TEAM DYNAMICS: IMPLICATIONS FOR RECRUITMENT AND RETENTION OF MINORITIES

Sandra C. Quinn, PhD, is the Associate Dean for Public Health Initiatives at the University of Maryland. She is also the Principal Investigator on Building Trust between Minorities and Researchers: A Bioethics Research Infrastructure Initiative funded by the National Center for Minority Health and Health Disparities (NCMHD).

As a foundation for her discussion, Dr. Quinn utilized some data from the Bioethics Research Infrastructure Initiative: Building Trust between Minorities and Researchers, funded by the National Institute on Minority Health and Health Disparities and the Office of the Director, NIH. The issues of race and racism were explored as they present in the team and impact recruitment, as well as the solutions for addressing these challenges.

1. Dr. Quinn discussed the relationships between PIs and staff and the ability to leverage diversity of knowledge, capability and experience on their team. New information in the literature describes the dynamics between PIs, IRBs and staff. The study examined 424 responses, 1/3 PIs; 1/3 staff; 1/3 IRB; participants were 78% male. If there are differences of opinion, all voices can still learn from each other. Cultural sensitivity does not apply solely to the PI, but the staff need it as well. Staff should be able to speak up, and staff/investigator interactions should be increased or improved.
2. This approach can be widely applied to enhance trials, as it is not specific to any one group or type of study. What is needed is a group dialogue that is candid and authentic. Group learning venues are environments to share ideas and best practices. It is probably not able to enhance study design, but rather enhances study effectiveness.
3. Retention is dependent on relationships with staff –PIs and staff both need to feel respected. Staff must be able to share ideas and help each other. A strong case is made for cultural competency building and allowing time to build rapport between patients and staff, which will ultimately improve retention.
4. Patients need follow-up with research outcomes. The main challenge is how to engage people to want to learn about and understand the impact of cultural differences. They need more than matching gender and skin color, but rather allies who are capable and confident with various populations. Group learning and candor are critical. There is a misperception that minorities are concerned with the race of their physician. A study of 2,400 African-Americans and Hispanics indicated in large numbers that this was not a concern, thus it is not so important to match demographics, but rather improve rapport and sincerity. If enough trainers can be found, they can empower research teams. Training for the research team, however, needs high interaction.

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#### POSTMARKET STUDIES USING SURGICAL MESH EXAMPLE

Mary Beth Ritchey, PhD, MSPH, is an Epidemiologist at FDA.

At the time of the medical product approval, there may be a continuing need for additional clinical evaluation to evaluate longer-term performance, use within the community, training programs for medical product use, evaluation of sub-groups, or assessment of rare adverse events and real world use. These Phase IV or “postmarket” studies often have difficulty recruiting and retaining participants. In addition, those who continue to participate may not reflect the real world use that these studies intend to capture. Evaluation of published literature and adverse event reporting, establishment of registries, and assessment of administrative medical billing data may be used in the postmarket environment to augment evidence collection and focus questions evaluated via *de novo* clinical studies.

Using surgical mesh as an example, Dr. Ritchey discussed recruitment of women in postmarket studies, the effects of study design and execution, findings from literature and adverse events that have been used to focus study questions for surgical mesh, and novel use of registries and claims data for assessing the outcomes women have with this device.

1. Many types of surgical mesh are used in cervical surgery. Postmarket studies gained information from literature, advocacy groups, and MAUDE (Manufacturer and User Facility Device Experience) adverse event reports. The surgical mesh study involved novel ideas and brought in new data. Investigators and patients must talk through the issue of informed consent. A need was recognized for informed consent that addresses technical aspects of surgery and risk information. There are known issues, but no denominator data about the population.
2. Hopefully, the findings will lead to the development of better clinical trial design. A well-written, informative, appropriate reading level informed consent form (ICF) should work for all trials. By improving design of consent forms, more information can be obtained from patients.
3. Better ICF could improve enrollment of women and minorities by increasing trust through transparency and increased confidence in the system and the federal regulators.
4. Investigators could use a survey of all the women that have had the device implanted. There is difficulty in writing a consent form that has such complicated information at a level that “my mother can understand.” At the same time, patients do not want to be talked down to by their investigators.

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#### CHALLENGES OF COLLECTING DATA ON MEDICATION USE IN PREGNANCY

Leyla Sahin, MD, is a Medical Officer on the Maternal Health Team at FDA’s Center for Drug Evaluation and Research. The mission of the Maternal Health Team is to help women and their healthcare providers make well-informed medicine choices when medicine is needed during pregnancy or breastfeeding.

Pregnant women are a challenging population to study due to concerns regarding potential adverse effects of medication exposure on the developing fetus. Approximately 64% of pregnant women in the U.S. are given prescriptions for chronic medical conditions or acute problems that arise during pregnancy.<sup>99</sup> This table talk discussion focused on the challenges of obtaining data on medication use in pregnancy. The discussion included some of the scientific, regulatory, and ethical considerations of including pregnant women in clinical trials. There was also a discussion of pregnancy registries as a way to collect data in pregnant women without incurring any intervention-associated risk. Sahin also provided a case study of higher morbidity and mortality among pregnant women infected with H1N1 influenza.<sup>100</sup>

To justify enrollment of a pregnant woman in a clinical trial, the treatment must provide a direct benefit to the pregnant woman, particularly in life-threatening diseases without other interventions. In contrast to clinical trials, pregnancy exposure registries collect health information from women who take medicines or vaccines when they are pregnant. The observations from the registry provide valuable data without raising ethical concerns for a sponsor.

1. Registries are a useful tool gathering post-marketing data. Wider use of registries may reduce the need for large drug intervention trials in pregnant women.
2. The FDA Amendments Act of 2007 now requires pregnancy registry for drug approval. The priority

for recruiting women to pregnancy registries is through their doctor or pharmacist, but the sponsor does not need to provide a great deal. When a pregnant woman is prescribed a drug by her physician, she should be made aware of the pregnancy registry.

3. As pregnancy registries generally collect information by phone interview, there is little concern for withdrawal from the study.
4. Outreach for pregnancy registries could be done through churches or schools. Pharmacists should be involved in spreading awareness of pregnancy registries.

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<sup>99</sup> Andrade S. E., et al. Prescription use in pregnancy. *Am J Obstet Gynecol.* 2004; **191**:398-407.

<sup>100</sup> Goldkind S. F., et al. Enrolling pregnant women in research - lessons from the H1N1 Influenza Pandemic. *New England J Med.* 2010 Jun 17; **362**(24):2241-3.

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## INTERNATIONAL CLINICAL TRIALS AND DIVERSITY: CHALLENGES

Mary F. Tobin, PhD, is a Managing Director of IMPACT LLC, a professional services firm serving Life Sciences industry clients and the U.S. Federal Government's HHS Operating Divisions, including FDA. Matthew D. Whalen, PhD, is a Principal of IMPACT LLC, and serves on the Board of Trustees Nominating Committee at the Association of Clinical Research Professionals.

Challenges discussed:

- ◆ Understanding the role that culture plays – domestically, internationally, and cross-nationally – throughout the clinical trial process; and employing cultural competencies in study design and recruitment through risk evaluation and mitigation
- ◆ “Offshoring” clinical research and implications for minorities and women, domestically and internationally
- ◆ Designing international trials to benefit underserved global populations and avoiding abuses especially from the perspective of ethical considerations such as social and scientific value, vulnerable populations, and respect for enrolled subjects
- ◆ Utilizing clinical research as a priority for country and community economic development, especially in developing and redeveloping countries, while addressing the intended and unintended consequences of harmonization and meeting and abiding by international standards
- ◆ Creating and leveraging mechanisms of public/private sector partnerships that have become internationally-favored methods for working effectively and dealing transparently across borders

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## INCLUSION OF WOMEN IN EARLY PHASE CLINICAL TRIALS

Lei Zhang, PhD, is Special Assistant to Office Director, Office of Clinical Pharmacology, FDA Center for Drug Evaluation and Research.

In 1993, FDA issued guidelines recommending safety and efficacy analyses by gender, age, and race in clinical trials for drug applications. Recently FDA studied inclusion of women in early phase clinical trials in drug or biologics applications approved by FDA between 2007 and 2009. The database included 925 clinical trials conducted over the past decade for 62 new molecular entities (NMEs): 50 New Drug Applications (NDAs), and 12 Biologic License

Agreements (BLAs). All NME submissions studied contained at least one early phase clinical trial that enrolled women. Overall, 36% enrolled were women. The analysis showed that the inclusion of women in early phase clinical trials submitted to FDA has improved over the time period studied. Overall, the percentage of women enrolled in clinical trials has increased significantly over the past decade, although it remains below 50%. This study was discussed in depth during this table talk.

1. By encouraging focus on women in Phases I and II, a sponsor is more likely to detect early side effects related to body size or hormones and adverse events. To address these data requirements early, enables the sponsor to understand these effects before large Phase III trials; basically, it helps to reduce uncertainties. Clinical pharmacology and early knowledge can be used to better address risks, based on molecular type.
2. Clearly, looking at women and minorities early will help with dosing/adverse events. It enhances the data and the outcomes learned from the trial and helps toward the design of the Phase III trial. It provides sponsors with the tools needed to be allies in patient safety – they should work with FDA early and share early data. The more we learn on drug absorption, distribution, metabolism, excretion, the more we can inform drug dose/frequency and safety in women to project future risk.
3. Sponsors could gain greater trust from women and minorities if they believe that the study is being carried out thoroughly and with their health interests in mind – greater trust could increase recruitment and/or retention. By pooling more raw data (commonly done in the European Union) sponsors will learn more, increase safety and improve outcomes.
4. Manufacturers still want to make one-size-fits-all, and also don't want to have to make many different dosages. This challenges providers who realize they need to adjust the dose for a patient due to his/her gender and/or ethnicity, knowing that the full dose causes side effects; however, pill splitting is not really the answer. How can this be accomplished without imposing an insurmountable financial and time burden on companies already in danger of failing?