

# Cultural competent clinical trials - 'a continued commitment to human subject protection'

## Abstract

In the days to come numerous Americans will be faced with an unprecedented issue—that of becoming medically insured as mandated by new legislative healthcare reform. The Affordable Care Act was passed by Congress and then signed into law by the President on March 23, 2010. On June 28, 2012 the Supreme Court rendered a final decision to uphold the health care law<sup>1</sup> to this end individuals from diverse ethnicities will become recipients of insured healthcare, many for the first time. This new state of affairs for the healthcare industry will undoubtedly have an impact on the healthcare delivery systems including the clinical trials industry. Clinical research professionals will need to enhance their skill sets to ensure that diverse and ethnic populations including limited English proficient individuals, are not only welcomed and protected study participants in research trials but that the differing characteristics of these same volunteers are included in the design of the respective trial with a goal of expanded generalizable knowledge. Successful adaption of these two qualities will depend heavily on the researcher's ability to embrace this shift change in subject population diversity. In this article, special attention will be given to limited English speaking populations. The author argues that early intervention and implementation of cultural competency awareness will be one of the leading factors contributing to development of human subject protection best practices for the 21st Century clinical trials professional.

**Keywords:** diversity, clinical trials, human subject protection

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**Abbreviations:** FDA, food and drug administration; OHRP, office of human research protections; NBAC, national bioethics advisory commission; LEP, limited english proficiency; OMH, offices of minority health

## Background

Individuals entering the field of clinical research for the first time as well as ongoing research professionals are often required to complete comprehensive training prior to participating with a federally regulated research study. Some institutions mandate training annually or at minimum bi-annually. Traditionally, at some point in this training, most individuals are exposed to the historical events that have led to the established framework of current laws, guidelines, and regulations which have led to the principles of good clinical practice as it pertains to human subject protection and sound ethical conduct in medical research. Familiarity with the events of the Nuremberg Trials, the Tuskegee Syphilis Study, with the subsequent renderings of the Declaration of Helsinki and the Belmont Report have found permanent homes in those involved in clinical trials. Many know the stories well. The resulting contiguous principles promulgated in support of these infamous historical milestones are more than just magnifiers of past wrong doings. They do not just enlarge mere researcher misconduct. The unrelenting bottom line has and always should be protection of the rights, welfare, and safety of study subjects—especially those that fall into the category of vulnerable populations.

## Introduction

### What are vulnerable populations?

The Food and Drug Administration (FDA) regulates clinical

investigations of products under its jurisdiction. These rules are published in the Code of Federal Regulations. There are numerous references for human subject protections as well as protection of vulnerable populations including Title 21, CFR part 50, for informed consent, Title 45 CFR 46 Subpart B, prisoners, Title 45 CFR 46 Subpart C, and children Title 45 CFR 46 Subpart D, 21 CFR 50 Subpart D. Title 21CFR part 50, Protection of Human Rights was issued in 1980, amended in 1981, 1989, 1990, 1991, 1996, 1997, 1999, 2006, and 2011, applies to informed consent by research subjects.<sup>2</sup> For clinical trials under its jurisdiction, the U.S. Department of Health and Human Services has delegated a leadership role to the Office of Human Research Protections (OHRP). OHRP provides guidance and regulatory oversight on rights, welfare, and wellbeing of research subjects.

Federal regulations identify specific categories such as pregnant women, fetuses, neonates, prisoners and children as 'vulnerable' and deserving of special protections. However, there are other populations that may also be subject to coercion in the clinical research process and be equally deserving of special protections. One suggested definition for vulnerability is the degree to which people are susceptible to be harmed, degraded, destroyed, or exposed to hostile factors<sup>3</sup> in furtherance of this definition, the National Bioethics Advisory Commission (NBAC) which existed from 1996 to 2001 under the leadership of President Clinton, proposed six categories for the term vulnerability. NBAC received its authority under Executive Order 12975, Public Law 92-463, as amended (5 U.S.C. Appendix 2) and was charged as one of the first priorities to direct its attention to consideration of 'protection of the rights and welfare of human research subjects'.<sup>4</sup>

**The resulting vulnerability categories follow:**

- i. Cognitive or Communicative Vulnerability
- ii. Institutional Vulnerability
- iii. Deferential Vulnerability Medical Vulnerability
- iv. Economic Vulnerability and Social Vulnerability.<sup>5</sup>

Table 1 outlines the six categories of vulnerability with an added definition and or example. Certain populations and certain prospective research subjects may exhibit multiple types of vulnerability (for example, participants may be indigent, adversely ill, and non-English speaking). Protocols must address each of the vulnerabilities presented

by the specific study population. Some of the more commonly known vulnerable populations such as children and pregnant women are subpopulations which many academic researchers have great familiarity. For example, pediatric oncologists are well inculcated on their target population's needs and much more adept on how not to conduct themselves when engaged in clinical studies. A less familiar vulnerable subgroup however, involves individuals who do not claim English as their primary language. From a statutory standpoint this category of individuals is categorized as Limited English Proficiency (LEP) individuals and supported by Federal laws particularly applicable to language access which includes Title VI of the Civil Rights Act of 1964, and the Title VI regulations, prohibiting discrimination based on national origin.<sup>6</sup>

**Table 1** Six Categories of Vulnerability as proposed by the National Bioethics advisory commission

Type of vulnerability	Definition of prospective study subject
Cognitive or Communicative Vulnerability	Insufficient ability to understand information; they could also lack capacity as a result of a medical emergency; (i.e. non-speaking English individual)
Institutional Vulnerability	Available cognitive capacity to consent but are subject to the formal authority, (i.e., prisoners)
Deferential Vulnerability	Available cognitive capacity, but informal power relationships may heighten the risk that the individual's decisions will not be truly voluntary, (i.e. parents who regularly defer to the wishes of their adult children)
Medical	Serious health conditions for which there are no satisfactory standard treatments (e.g., metastatic cancer or rare disorders). There's an increased the risk that informed consent might be based on misunderstanding potential benefits or might be motivated by a desire to find a treatment. Opportunities for increased exploitation due to unreasonable expectations about the potential benefits.
Economic	Cognitive capacity to consent but are disadvantaged in the distribution of social goods and services such as income, housing, or health care. Presents a potential for an undue inducement to enroll.
Social	Social vulnerability is a function of the social perception of certain groups, which includes stereotyping and can lead to discrimination. In any case, the perceptions devalue members of such groups, their interests, their welfare, or their contributions to society <sup>5</sup>

That being stated, the progressive influx of vulnerable population growth has yielded a multifaceted subpopulation of diverse individuals. Changing healthcare regulations concerning mandated healthcare coverage more now than ever have the potential to create a tangible and visible shift in the landscape of vulnerable population participation in clinical trials. One of the new consumer protections offered the general public under this new legislation is ensuring coverage for individuals participating in clinical trials. Insurers will be prohibited from dropping or limiting coverage because an individual chooses to participate in a clinical trial. This piece of legislation applies to all clinical trials that treat cancer or other life-threatening disease or condition and becomes effective January 1, 2014.<sup>7</sup> In essence, insurers may not discriminate against covered individuals who choose to participate in clinical trials. Ten years ago the results of a study of NCI-sponsored cancer treatment trials found that uninsured patients represented only 5.4 percent.<sup>8</sup> Because the rate of participation in United States clinical trials correlates with the demographics of income, educational attainment, employment status, and insurance coverage, increased vulnerable population participation will more likely than not be on the rise in the years to come with mandated health coverage.<sup>5</sup> The time is ripe for the clinical trials network to become more proficient in the cultural competency side of human subject protections.

**Rapidly moving forward-the census bureau facts**

Review of the 2010 U.S. census bureau reports contrasting population growth over the past ten years, seems to point in the direction of a human 'color' palette change rapidly occurring in the U.S. The impact of this unfolding new generation of Americans will inevitably have an undeniable influential impact on the delivery health care as we now know it. "The past decade has shown an increase in the use of interpreting services at all major hospital and clinics throughout the nation. Language requirements are broader as our refugee resettlement increases and become more diverse. Title VI requirements have been highlighted nationally through the Office of Minority Health as well as through regulating and accrediting organizations such as JCAHO (<http://www.jointcommission.org>)".<sup>9</sup>

According to the U.S. census bureau, examination of racial and ethnic group distributions nationally shows that while the non-Hispanic white alone population is still numerically and proportionally the largest major race and ethnic group in the United States, it is also growing at the slowest rate.<sup>10</sup> Examination of the ethnicity population growth profile raises questions on correlative factors of English proficiency for the various diversities represented in the U.S.

## From census bureau facts to cultural competence

**According the US department of health and human services offices of minority health (OMH) cultural competency is:** Cultural and linguistic competence is a set of congruent behaviors, attitudes, and policies that come together in a system, agency, or among professionals that enables effective work in cross-cultural situations. 'Culture' refers to integrated patterns of human behavior that include the language, thoughts, communications, actions, customs, beliefs, values, and institutions of racial, ethnic, religious, or social groups. 'Competence' implies having the capacity to function effectively as an individual and an organization within the context of the cultural beliefs, behaviors, and needs presented by consumers and their communities.<sup>11</sup>

### Office of minority health supports the belief that culture and language could affect:

- i. Health and Healing.
- ii. How illnesses and their causes are perceived.
- iii. The behaviors and attitudes of those seeking health care providers.
- iv. The delivery of service by the provider who looks at the world through their own limited set of values, which can compromise access for patients for mother cultures.<sup>5</sup>

According to the Harvard Catalyst, 'cultural competence in research is the ability of researchers and research staff to provide high quality research that takes into account the culture and diversity of a population when developing research ideas, conducting research, and exploring applicability of research findings'.<sup>12</sup> In support of both of definitions, cultural competence places the responsibility on the practitioner for proficiently equipping themselves to engage in effective methods of health care delivery when faced with service delivery to sensitive and diverse ethnicities. The obligation to human subject protection through culture competency is best illustrated in the words of Martin Luther King, "Of all the forms of inequality, injustice in health care is the most shocking and inhumane".<sup>13</sup>

### Historical involvement of minority participation in clinical trials

Below is a short list of minority involvement in clinical trials that support the need for an adaptive behavioral change in the direction of a more cultural competent clinical research professional.

#### The findings are representative of various research initiatives

- i. 'NCI's Prostate Cancer Prevention Trial, which was conducted in 1993-2003, recruited only 8% minority participants of over 18,000 men enrolled'.<sup>5</sup>
- ii. 'A National Survey of cancer patients found that 85% of respondents were unaware that participating in a clinical trial was a treatment option for them'.<sup>25</sup>
- iii. Hispanics who made up 9.1% of the US population [2002 data] made up only 3% of participants in clinical trials in 2002, down from 3.7% in 1996.<sup>14</sup>
- iv. 'Enrollment in clinical trials is disproportionately low among African Americans/blacks and Hispanics/Latinos in NCI-sponsored surgical trials'.<sup>25</sup>

- v. Strict inclusion and exclusion criteria are a commonly reported barrier to trial participation. In a study of African American/Black cancer patients, only 8.3% were eligible for clinical trial participation due to the strict criteria. Nearly 20% were excluded due to co-morbidities. Individuals without health coverage will inevitably present with a greater degree of secondary illnesses.<sup>5</sup>
- vi. Many US trials require English proficiency for potential participants, automatically excluding those who do not speak the language. Language factors also pose a serious barrier to provider-patient communications and attempts to recruit individuals into clinical trials.<sup>5</sup>
- vii. "People don't know how important [diversity in clinical research] is," states a Project IMPACT (Increase Minority Participation and Awareness of Clinical Trials), principal investigator. There is a suggestion that different populations could have different adverse effects to the same medications, and therefore pulling these medications off the market without looking at all populations, hinders research discovery.<sup>15</sup>

### Becoming cultural competent proficient: behavioral changes for the clinical research professional

As noted earlier, numerous Americans speak more than one language. As of August 16, 2009, it is estimated that there were more than 10,900 recorded ongoing clinical trials seeking 2.8million study subjects<sup>16</sup> No doubt, the number of trials has increased since that time period as has the need for qualifying study subjects. As the number of trials increase, a proportionate need for acceptable study subjects will grow. Because of the changing ethnicity profile of Americans coupled with the influx of diverse populations as insured healthcare recipients, the racial identity of the clinical research volunteer will also inevitably take on a new dimension. Recommendations for meeting this new demand effectively are identified in the table below. The responsible party of the clinical trial team is also noted.

\*Language Identification flash cards provided by the Department of Justice; Retrieved from: [http://searchjustice.usdoj.gov/search?q=crt%20cor%20Pubs%20ISpeakCards&q=site%3Awww.justice.gov%2Fcr&sort=date%3AD%3AL%3Ad1&Output=xml\\_no\\_dtd&client=default\\_frontend&proxystylesheet=default\\_frontend&site=default\\_collection](http://searchjustice.usdoj.gov/search?q=crt%20cor%20Pubs%20ISpeakCards&q=site%3Awww.justice.gov%2Fcr&sort=date%3AD%3AL%3Ad1&Output=xml_no_dtd&client=default_frontend&proxystylesheet=default_frontend&site=default_collection)

Output=xml\_no\_dtd&client=default\_frontend&proxystylesheet=default\_frontend&site=default\_collection

¶Legally Authorized Representative means an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research Table 2. Written Translation is often referred to only by the term "translation," written translation is the rendering of a written text in one language in a comparable written text in another language. Sight translation: Sight translation is the oral rendition of text written in one language into another language and is usually done in the moment. (The National Council on Interpreting in Health Care-Revised March 2010, pp. 3-4); retrieved from: <http://www.ncihc.org/assets/documents/Translation%20Guidelines%20for%20Interpreters%20REVISED%2031710.pdf>

∞Interpreting is the oral rendering of spoken or signed communication from one language into another. Ibid. QA healthcare interpreter's primary duty is to convert oral communications from one language to another. Because some information needed by a patient or guardian may exist only in written

form, an interpreter may be called upon to communicate the written information orally in the client's language, or the client may need to have a durable written record of information that only the interpreter can provide. Wherever possible, in the interest of accuracy and efficiency, written texts in appropriate languages (or audio or video recordings of texts) must be prepared with the assistance of qualified translators in advance of their need in any particular provider-patient encounter Table 3.

£A certified interpreter is one who has taken and passed an examination administered by a knowledgeable authority. Credentials for professionally qualified interpreters require sufficient documentation and authentication, and must meet established criteria. Certified and professionally qualified interpreters are paid at a higher rate than language skilled/ad hoc interpreters. (US Courts; retrieved from: <http://www.uscourts.gov/FederalCourts/UnderstandingtheFederalCourts/DistrictCourts/CourtInterpreters/InterpreterCategories.aspx>)

**Table 2 A** broad sweeps of the statistical changes for some racial ethnicities from 2000 to 2010 as depicted on the US Census Bureau website

**HISPANICS**

More than half of the growth in the total U.S. population between 2000 and 2010 was because of the increase in the Hispanic population. Between 2000 and 2010, the Hispanic population grew by 43 percent, rising from 35.3million in 2000 to 50.5million in 2010. . . While the non-Hispanic white alone population increased numerically from 194.6million to 196.8million over the 10-year period, its proportion of the total population declined from 69 percent to 64 percent.

**ASIAN**

The Asian alone population grew faster than any other major race group between 2000 and 2010, increasing by 43 percent. The Asian alone population had the second-largest numeric change (4.4million), growing from 10.2million in 2000 to 14.7million in 2010.

**WHITES**

The overwhelming majority (97 percent) of the total U.S. population reported only one race in 2010. This group totaled 299.7 million. Of these, the largest group reported white alone (223.6million), accounting for 72 percent of all people living in the United States.

**BLACKS**

The black or African-American population totaled 38.9million and represented 13 percent of the total population in 2010. Ninety-two percent of people who reported multiple races provided exactly two races in that same year; white and black was the largest multiple-race combination.

**Geographical Summary**

In the 2010 Census, just over one-third of the U.S. population reported their race and ethnicity as something other than non-Hispanic white alone (i.e. "minority"). This group increased from 86.9million to 111.9million between 2000 and 2010, representing a growth of 29 percent over the decade.

Geographically, particularly in the South and West, a number of areas had large proportions of the total population that was minority. Nearly half of the West's population was minority (47 percent), numbering 33.9 million. Among the states, California led the nation with the largest minority population at 22.3 million.

Between 2000 and 2010, Texas joined California, the District of Columbia, Hawaii and New Mexico in having a "majority-minority" population, where more than 50 percent of the population was part of a minority group. Among all states, Nevada's minority population increased at the highest rate, by 78 percent.<sup>5</sup>

**Table 3** Language Identification flash cards provided by the department of Justice

Cultural competency recommendation	Responsible clinical trial team member
Study Design Strategy	Sponsor
Support Rationale	Clinical Trial Finance Office
Ensuring the inclusion of subgroups large enough to allow for subgroup analysis has an enormous impact on costs. In view of limited resources, the choice for a heterogeneous study population should at least be weighed against the strength of the indications for the presence of diversity in health outcomes. This implies that confronting diversity in clinical research starts with formulating hypotheses as to why diversity does or does not matter in a specific case.	Epidemiologist
	Investigator
When dealing with linguistically diverse populations, encourage the institutions access to use of 'I Speak'* Cards and or Telephonic Interpretative Services (TIS) for language challenged patients.	Study Coordinator,

Table Continued..

Cultural competency recommendation	Responsible clinical trial team member
<p>When enrolling language challenged ethnicities in high risk studies, ensure the ICF subject advocate or LAR¥ and subject have been alerted on how to contact the ICF emergency contact. Be watchful of informed consent forms that are overly complex as well as other study materials that may have a tendency to limit participation of an ethnic minority. Be willing to establish the proper training programs to ensure inclusion of qualified research staff.</p>	<p>Health care facility Administration Includes Clinical Trial Finance Office Facility Qualified Interpreter β</p>
<p>Review a translated ICF in advance with the Medically Qualified Interpreter prior to engaging the potential subject to ensure it is linguistically compliant with protocol mandates.</p>	<p>Study Coordinator  Investigator Institutional Review Board Qualified Translators Sponsor</p>
<p>When familiarizing language challenged as well as other ethnicities utilize 'teach back' skills in the informed consent process. Engage the potential subject in the training process to ensure understanding and compliance. Employ good clinical practice skills. Repeat procedure as needed.</p>	<p>Study Coordinator,  Institutional Review Board, Medically Qualified Interpreter, Sponsor, Investigator as needed</p>
<p>Before enrolling diverse ethnicities, if using subject diaries or other protocol mandated medical equipment, ensure the implements are ethnically linguistically compliant. Make all adjustments prior to study start. Ensure all implements are approved by the responsible IRB of record prior to study start. These steps must be taken not only to safeguard the welfare of the subject but to also ensure study compliance while minimizing attrition.</p>	<p>Study Coordinator,  Institutional Review Board,, Medically Qualified Interpreter, Clinical Trial Finance Office Sponsor, Investigator, as needed</p>
<p>Be Available, Genuine, Ethical and Professional Employ Good Clinical Practice at all times!</p>	<p>Sponsor, Investigator, Study Coordinator, Institutional Review Board, and Institutional Administrators-(Always utilize medically qualified interpreters£ and translators for federally funded clinical trials to ensure safety and welfare of subjects!)</p>
<p>Remember, in addition to obvious misconduct and lack of knowledge on the part of practitioners, health disparities can be affiliated with factors such as patients' perceived discrimination and mistrust in the health care profession which includes poor or ineffective communication between patients and physicians. Formulation and implementation of 'Best Practices' decrease liabilities for Sponsors and Institutions. Place a cultural competent initiative on your projected goals for the coming year, if one is not already in progress. There are numerous resources available and at your fingertips!</p>	<p>Among the important findings of a particular study examining language barrier were the differences in impact adverse events had on the LEP (Limited English Proficiency) versus the English-speaking patients. Some degree of physical harm occurred to 49.2. percent of the LEP patients that had reported adverse events, but only 29.5 percent of English</p>

Table Continued..

**Cultural competency recommendation****Responsible clinical trial team member**

Speakers suffered physical harm from adverse events. Further, among those that did suffer harm, 47 percent of LEP patients had moderate temporary harm or worse, compared to only 25 percent of English-speaking patients. The rate at which LEP patients suffered permanent or severe harm or death was 3.7 percent, compared to 1.4 percent.<sup>17</sup>

A study of errors in medical interpretation and their potential clinical consequences published in the journal *Pediatrics* found that errors by "ad hoc" interpreters (like family members and neighbors) are significantly more likely to have clinical consequences as compared with errors made by compensated hospital interpreters. The Joint Commission report concluded that "ad hoc" interpreters are more likely to omit or add information, insert their own values into the interpretation, or misinterpret the information.<sup>18</sup>

**Conclusion**

The burden for improvement in the realm of cultural competency in clinical trials should not be just a mere legislative concern. As key scientific health care service providers, clinical trial professionals share a duty and responsibility to embrace and uphold with ardent expression a commitment to the support of cultural awareness as it pertains to human subject protection. All segments of society should have the opportunity to participate in research, if they wish to do so and if they are considered to be appropriate participants for a given protocol, even though some individuals may need additional protections before they can fully participate in the research study. It is not enough that clinical researchers merely encourage diversity participation for the sake of numbers and appearance. Validation and expansion of generalizable knowledge in the execution of clinical research investigations is a must and can only come through inclusion of diverse populations in clinical studies. Being able to recognize the various types of vulnerable populations while providing adequate safe guards may prove a bit challenging at first but should be at the fore front of the clinical trial training process. Cultural competence is needed to make clinical research health care services more responsive to underserved and vulnerable populations.

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**Conflict of interest**

The author declares no conflict of interest.

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