

Surveying the Policy Landscape for Eliminating Disparities in Clinical Trials. *By Dan Bustillos JD, PhD (cand.)*

In an effort to orient our discussion at the September 2006 roundtable meeting of the EDICT Project in Houston, the following document has been prepared as a non-comprehensive yet broad survey of the existing laws, regulations, and guidelines that touch on the subject of diversity in clinical trial participation. This essay is intended as a survey of the policy landscape and attempts to trace the broad contours of this somewhat mysterious land where confusion and ignorance are no longer affordable. What I have explicitly left out of this short report is the various institutional policies that dot the landscape and hold sway over large swaths of the clinical trials enterprise. It suffices to note that it would be impossible in the space allotted to survey how individual institutions, sponsors, IRBs, and investigators may provide for greater protections or opportunities for candidate participants of their respective research than current laws and regulations provide.

The Nuremberg Code and the Declaration of Helsinki

While the ethics of medical research on human subjects is an ancient subject, it is impossible to speak of it in modern times without conjuring up the atrocities of Nazi human experimentation. Of this murder and mayhem was born The Nuremberg doctor's trial and its attendant Nuremberg Code. As such, it remains the conceptual fountain from which all subsequent attempts to regulate human subjects research stem. It famously commands that "the voluntary consent of the human subject is absolutely essential."¹

The heir-apparent of the Nuremberg Code is the Helsinki Declaration published by the World Medical Association in 1964. At first glance it seems to be merely an update to the by-then dated Nuremberg Code, but a closer inspection shows that the terrors of the Nazi concentration camps were no longer so fresh on the policymaker's minds. The Helsinki Declaration belies a benign view towards medical research as it was written by and for medical researchers. However, the policy's less-than-absolute language has proved more practical for medical progress while still ensuring that studies receive proper review.

The NIH Revitalization Act of 1993

While most other laws related to the ethics of human subjects research have historically been promulgated as a response to ethically deplorable cases (i.e.: Tuskegee Syphilis Study, Nazi experimentation, etc.), the NIH Revitalization Act's inclusion clause stems more directly from a larger social shift in thinking about issues of gender, ethnicity, and race.

The Civil Rights Movement and the Women's Liberation Movement spawned a vigorous debate nationally about social

justice issues concerning race and gender, and brought an awareness of these group's historically unfair participation in clinical trials. Originally, women and the underprivileged bore more than their fair share of the burden of medical research.² Then, after scandals such as the Tuskegee Syphilis Study changed the human subject protection's landscape, these groups became *underrepresented* in clinical trial populations. The most noted example of this may be the glaring failure to include women in cardiovascular disease prevention trials such as MRFIT and the Physician's Health Study.³

These injustices resulted in various policies and laws crafted in the early 1990s in the U.S.. Among these, perhaps the most impactful has been the 1993 NIH Revitalization Act (Public Law 103-43).⁴ Among its many other provisions, the NIH Revitalization Act significantly strengthened the NIH policies regarding the inclusion of women and minorities into clinical trial populations. Enacted in March 1994, the law states that:

It is the policy of the NIH that women and members of minority groups and their subpopulations must be included in all NIH-

supported biomedical and behavioral research projects involving human subjects, unless a clear and compelling rationale and justification establishes to the satisfaction of the relevant Institute/Center Director that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research. Exclusion under other circumstances may be made by the Director, NIH, on the recommendation of an Institute/Center Director based on a compelling rationale and justification. Cost is not an acceptable reason for exclusion except when the study would

duplicate data from other sources. Women of childbearing potential should not be routinely excluded from participation in clinical research. All NIH-supported biomedical and behavioral research involving human subjects is defined as clinical research. This policy applies to research subjects of all ages. [...] NIH funding components will not award any grant, cooperative agreement or contract or support any intramural project to be conducted or funded in Fiscal Year 1995 and thereafter which does not comply with this policy.⁴

The NIH Revitalization Act has needed periodic clarification as to its specifics, but its overall goal of better representation of certain currently underrepresented groups is clear. The Act also makes use of the Office of Management and Budget's definition of minority

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groups for federal reporting. The four groups include American Indian/Alaska Native, Asian/Pacific Islander; Black/African American, not of Hispanic origin; and Hispanic. The definition acknowledges the diversity within these groups by using the disclaimer: “and their subpopulations”, but many commentators have attacked the OMB standards as being too abstract, inaccurate, and leaving out some important groups that are in need of protection (e.g.: Appalachians).

FDA Modernization Act of 1997

Spurred on in part by the NIH Revitalization Act, The Food and Drug Administration (FDA) attempted to fill a gap that the NIH policy left in its wake. Since the NIH policy only affected NIH-funded trials, many privately-financed studies did not come under its purview. However, if these studies would ever be used in support of an application to the FDA for approval of a biologic, drug, or device, then they must conform to FDA requirements.

Thus, the Food and Drug Administration Modernization Act of 1997 (FDAMA), Section 115 Clinical Investigations (b) Women and Minorities - was amended to read: “The Secretary shall, in consultation with the Director of the National Institutes of Health and with representatives of the drug manufacturing industry, review and develop guidance, as appropriate, on the inclusion of women and minorities in clinical trials [...]”⁶

In 1993, the FDA reversed a long-standing guideline that summarily excluded women of childbearing potential from early drug studies that did not target serious or life-threatening diseases.⁷ Unlike this explicit regulatory barrier to the participation of women, the FDA found that minorities have never been the object of a regulation that excludes them from research. Because of

this and the fact that conclusive evidence was not readily found by the FDA, the final recommendations were far too tentative in the opinion of many commentators.⁸ For instance, the FDAMA does not regulate the conduct of clinical trials and does not require the inclusion of particular groups, but merely required sponsors to report the number of minorities enrolled in clinical trials annually. In fact, the guidance seemed to suggest quite illogically that since no evidence was found that the barriers to enrollment of minorities in research are regulatory in nature, then they could not be addressed by regulatory guidance.⁹

Table 1. NIH Revitalization Act of 1993

Core Idea	Announces the revised NIH policy on recruitment of women and minorities into NIH-funded, Phase III clinical trials
Concerns that Prompted the Act	<ul style="list-style-type: none"> • The under-representation of women and minorities either because they are excluded <i>per se</i>, because of unduly restrictive inclusion criteria, or because of a failure to remove barriers to access. • Lack of attention paid to health issues peculiar to these groups when designing clinical research studies.
Summary of the Act	<p>This law requires investigators on NIH-funded, phase III clinical trials to include women and minority populations in their research unless one of the following applies:</p> <ul style="list-style-type: none"> • There is clear and compelling evidence that the research poses a significant risk to the health of subjects justifies their exclusion (Note: However, women <i>cannot</i> be excluded from a trial simply because they may become pregnant during a trial that could pose a serious risk to the health of the mother and/or fetus). • The inclusion is inappropriate with respect to the purpose of the research (e.g.: women can be excluded from prostate cancer trials) • The inclusion is inappropriate under such other circumstances as the Director of the NIH may designate. • If there is substantial scientific data demonstrating that there is no significant difference in effects on women or minorities with respect to the drug or procedure being studied • A controversial requirement of this regulation is that cost cannot be a consideration in whether inclusion is appropriate. • The Act also requires that the study design must provide for a valid analysis of any differences the study may have shown for women and minorities. • The NIH Revitalization Act only applies to NIH-funded research. Much clinical research, however is privately funded and not under the aegis of the this Act (However FDA regulations were promulgated to “fill” this gap). However, it is common, in large, multicenter clinical trials, for research coffers to co-mingle private and NIH funds--which then means that both NIH and FDA regulations apply.

Until recently, it was widely thought that the mandate of equity in gender and minority accrual in the NIH Revitalization Act of 1993 applied only to phase III *therapeutic* trials. This myth that was being perpetuated within the clinical trials enterprise was finally debunked by a report in November, 2005 that unambiguously stated that accrual to non-therapeutic trials should be the object of scrutiny along with therapeutic trial enrollment.⁵

However, it would be a mistake to say that the FDAMA is impotent on the issue of disparities in clinical trials. For example, if a sponsor fails to provide adequate data on minorities, the FDA's Center for Drug Evaluation and Research (CDER) may refuse to file a new drug application for lacking safety and efficacy data for "the population intended to use the drug, including pertinent subsets, such as gender, age, and racial subsets" required by the Food, Drug and Cosmetic Act.¹⁰ Refusal based on the lower threshold of data collection, however, seems to be quite rare.

In 1999, the FDA issued guidance to industry in a report entitled "Population Pharmacokinetics" that recommends the use of population pharmacokinetics in drug development to help identify differences in drug safety and efficacy among population subgroups.¹¹ This policy is described in the September 2005 FDA report: *Guidance for Industry: Collection of Race and Ethnicity Data in Clinical Trials*¹² which follows the same rubric for FDA inclusion policies: (1) encourage sponsors to be inclusive in research, and (2) require applicants to report raw numbers and percentages of minority participants and their gender. No penalty accrues to researchers who have "unacceptable" participant demographics.

CDC Guidelines

The Centers for Disease Control (CDC) also have a policy on the Inclusion of Women and Racial and Ethnic Minorities in Externally Awarded Research.¹³ Enacted in 1995, the CDC policy for Inclusion is remarkably similar to the NIH Inclusion policy. It attempts to ensure that research being funded by the CDC is inclusive as to gender, race, and ethnicity whenever feasible and appropriate. Cost may not be a factor in the deliberation of the appropriateness of the inclusion and the definition of race and ethnicity is taken from the OMB. Women of childbearing potential cannot be routinely excluded from CDC-sponsored research. One important difference is that the CDC policy gives substantial guidance as to remedies for low accrual and prompts researchers to identify gaps in knowledge about health problems suffered by women and minorities and then address these problems.

CIOMS Guidelines

Until quite recently, regulations and guidelines have kept silent on the subject of post-trial benefit to the participants and their communities. In 1993 the Council for International Organizations of Medical Sciences first "codified" the notion that sponsors and researchers should provide the participants of the trial access to the approved products of the study after the trial concludes.¹⁴ It wasn't until the late 1990s, when the ethics of international HIV trials became prominent, that international guidelines began mandating that all international trials should provide for post-trial benefits to participants.¹⁵ This has proved controversial and difficult both to achieve practically and to regulate—especially when the conceptually and practically distinct notion of providing post-trial benefit to the participants in the trial and to that participant's wider community are conflated.¹⁶ Since this rocky start, new guidelines have become more diligent in including provisions for post-trial benefit, and clearer as to what is expected of the researcher. For example, the 2000 revision of the Declaration of Helsinki declared that "[a]t the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic, and therapeutic methods identified by the study."¹⁷

Unfortunately, the regulations and codes that now make the duty to provide post-trial benefit to international research participants suffer from two major flaws: (1) they do not apply to the majority of trials being conducted domestically by a sponsor, and (2) they provide no specifications as to how sponsors and researchers are to provide the post-trial benefit.¹⁸ There are, however, some models existing as to how sponsors can partner with local governments and healthcare providers to assure access to study drugs after a trial, but there is need for much improvement.¹⁹

Today, clinical trials are regulated by what one writer has deemed "a crazy-quilt of hortatory codes and maxims, scattered federal laws and regulations, and most importantly, by Institutional Review Boards, which provide peer review of proposed experiments."²⁰ This "crazy quilt" does, however, provide the foundational landscape from which better policy can be crafted to research, report, monitor, and enforce the inclusivity of clinical trials. ●

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