



History of NIH Revitalization Act of 1993 and Current Relevance to Inclusion of Underrepresented Populations in Clinical Research

*From the EDICT (Eliminating Disparities in Clinical Trials) Project
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Abstract: *Historically, policies concerning ethical issues in clinical research focused on the protection of research subjects from bearing an unfair burden of participation in research. It now appears the pendulum is swinging in the opposite direction and the ethical principle of justice calls for appropriate inclusion of underrepresented populations in clinical research. The NIH has exhibited a pattern of nonenforcement of policies concerning inclusion of women and minorities in clinical research. However, there is recent movement toward policy refinements indicate that arguments of social justice are being heard and are working their way through the maze of health policy toward eliminating disparities in clinical trial participation.*

Historically, policies concerning ethical issues in clinical research focused on the protection of research subjects from bearing an unfair burden of participation in research as exhibited by the Syphilis Study at Tuskegee, contraceptive studies involving Latino/Hispanic women, and numerous studies on prison populations. However, now it appears the pendulum is swinging in the opposite direction and the ethical principle of justice calls for appropriate *inclusion* of underrepresented populations in clinical research. This calls for revisions to our current policies that guide clinical trial design and participation.

In 2005 the Chronic Disease Prevention and Control Research Center at Baylor College of Medicine created the Eliminating Disparities in Clinical Trials or EDICT Project. The EDICT Project was developed to design practical and realizable policy solutions that can be implemented in the public, private and non-profit

sectors, aimed to eliminate disparities in clinical trial participation.⁽¹⁾ It may take some time for EDICT recommendations to be implemented by local organizations, investigators and even incorporated into state and federal regulatory policies. The challenges of eliminating disparities of any type through health policy are evidenced by the historical account of enactment of the 1993 NIH Revitalization Act which strengthened NIH policies regarding the inclusion of women and minorities into clinical trials.

In 1984, U.S. Assistant Secretary for Health, Edward Brandt, M.D., directed the Public Health Service to create a Task Force on Women's Health Issues. The Task Force was chaired by Ruth Kirschstein, M.D., Director of the National Institute of General Medical Sciences with the assignment of reexamining the agencies' activities directed toward improving women's health.⁽²⁾ The Task Force submitted their report later that year to Dr. Brandt who subsequently issued

a memorandum to all Health and Human Services (HHS) directors to develop plans for implementing the recommendations of the Task Force. The Director of NIH then established the Advisory Committee on Women's Health Issues charged with responding to the recommendations published in the Public Health Service Task Force report.⁽³⁾ The work of the committee led to an NIH policy announced in 1986 that *encouraged* grant applicants to consider the inclusion of women in the study populations of all clinical research efforts.

In a similar fashion, the Secretary's Task Force Report on Black and Minority Health was issued in August 1985.⁽⁴⁾ The task force was created to investigate the health problems of blacks, Native Americans, Hispanics, and Asian Americans and Pacific Islanders. The Office of Minority Health was established in December of 1985 specifically to implement recommendations contained in the report focusing on minority health problems, delivery of health

services, increasing minority health professionals and the development of more complete data on minority health problems and increased research efforts.

A memorandum issued by NIH in 1989 again *urged* funding applicants to consider inclusion of women in study populations and recommended that publications resulting from NIH-supported research state the gender of the population used for the study.⁽⁵⁾ The memorandum also expanded the policy to recommend inclusion of minorities in research studies noting that the under representation of minorities in research studies “resulted in significant gaps in knowledge.”⁽⁶⁾ The policy recognized “there are clear scientific and public health reasons” for including minorities in research in order to “assure appropriate emphasis” is placed on “health problems that disproportionately affect” minority populations.⁽⁷⁾ Dismayed by perceived lack of interest in implementing the policy on inclusion of women and minorities in research, the Congressional Caucus for Women’s Issues, co-chaired by Rep. Pat Schroeder (CO) and Rep. Olympia Snowe (MA) and with the support of Congressman Henry Waxman (CA), requested the U.S. Government Accounting Office conduct a study on the problems in policy implementation at NIH. The GAO report, released in July 1990, documented that in the three years following the original policy announcement, NIH had made “little progress” in effectuating changes in the inclusion of women in clinical research.⁽⁸⁾ Specifically, the GAO found that: The policy had not been communicated to the research community. For example, the grant application booklet had not been revised to instruct applicant about the policy on women.

- The NIH policy only applied to extramural research and not to the intramural research program.
- Any advances that had been made

in policy implementation were inconsistent across divisions.

Following the issuance of the GAO report, the Congressional Caucus on Women’s Issues introduced the Women’s Health Equity Act of 1990 (WHEA).⁽⁹⁾ This legislation consisted of twenty separate bills aimed at improving research on women’s health issues, women’s access to health care, and disease prevention for women. The chief sponsor of this Act, Senator Barbara Mikulski, attached three provisions to legislation reauthorizing NIH funding which created an office specifically devoted to women’s health research at NIH, required that women be included in clinical trials, and established five contraceptive and infertility research centers. Of all the provisions included in the bill, only two were passed at that time. The GAO report also prompted the NIH to promulgate a new policy governing the award of federal research grants: “Applications for grants and cooperative agreements that involve human subjects are *required* to include minorities and both genders in study populations so that research findings can be of benefit to all persons at risk of the disease, disorder or condition under study.”⁽¹⁰⁾ The Congressional Caucus for Women’s Issues continued to leverage the GAO report to address women’s health care issues in the following years. In the 101st and 102nd Congresses in 1991 and 1992 respectively, Congress passed an NIH reauthorization bill containing budget increases for women’s health initiatives, established the Office of Research on Women’s Health as well as establishing various research centers within NIH. However, in both legislative sessions the bills were vetoed by then President George H.W. Bush, primarily because the legislation contained language regarding reproductive rights for women and authorized research utilizing fetal tissue.⁽¹¹⁾

In November 1992 Bill Clinton defeated incumbent George H.W. Bush in the presidential election, taking office in January 1993. Once again, in the 103rd Congress, the NIH Revitalization Act was introduced in the House of Representatives by Henry Waxman (CA) and in the Senate by Senator Edward Kennedy (MA). On February 3, 1993 Representative Henry Waxman chaired a Congressional hearing before the House Subcommittee on Health and the Environment of the Committee on Energy and Commerce to discuss the NIH Revitalization Act, which at the time was being debated in both the Senate and the House.⁽¹²⁾ The Act by this point was breathtaking in scope, addressing everything from ethical use of animals in research, research integrity, and AIDS research and was referred to by one legislator as “170 pages of set-asides, research centers and research mandates for specific diseases.”⁽¹³⁾ Thus, the inclusion of women and minorities in clinical research represented only a small portion of the proposed legislation. Two major points of disagreement concerning this bill were Title XX, Sec. 2007 adding acquired immune deficiency syndrome (AIDS) to the list of infectious diseases that would exclude an individual from immigration to the U.S. and even more divisive, Title I, Sec. 113 nullifying the moratorium on use of human fetal tissue for therapeutic purposes. The level of concern over research involving fetal tissue is expressed by Representative Bliley (VA) during his remarks in the February hearing stating he could not “in good conscience support the decision to allow such research to move forward with Federal funds.”⁽¹⁴⁾ Although the bill was passed overwhelmingly in the Senate, many in the House of Representatives voted against the legislation on the single issue of allowing fetal tissue to be used in research. From the floor of the House, Representative Bereuter (NE)

explained he voted against the bill on May 26, 1993 primarily because it would “overturn a moratorium on Federally funded fetal tissue transplant research from induced abortions.”⁽¹⁵⁾ Although there were others who shared the position of these legislators, Secretary of Health and Human Services (HHS) Donna Shalala, testifying at her first congressional hearing, emphasized the “administration fully supports the legislation” and that it was a “high priority” within the recently assembled Clinton regime.⁽¹⁶⁾ Her testimony reinforced the ideal that research on women and minorities should be integral to the disease discovery process. It was anticipated that the policies outlined in the NIH Reauthorization Act would ensure that the NIH would not revert back to a pattern of nonenforcement of their own policies concerning inclusion of women and minorities in clinical research.

In light of the controversial legislative history of inclusion of women and minorities in clinical trials, it is appropriate and necessary today to revisit the effectiveness of the statutory requirements and regulatory oversight by the NIH. It is encouraging to read that subsequent to enactment of the NIH Revitalization Act of 1993, a review of new phase III clinical trial proposals by the NIH revealed that “in only a few cases were projects not in compliance.”⁽¹⁷⁾ Further, a more extensive analysis of extramural research protocols funded in FY 1997 revealed that more than one-half of the six million enrollees were female, seventeen percent were Black and almost eight percent Hispanic.⁽¹⁸⁾ However, there are significant limitations to the interpretation and extrapolation of this data. For example, even as early as 1999 it was estimated that as much as 80% of all pharmaceutical clinical trials were funded not by NIH but by private industry, thus not subject to

the inclusion regulations.⁽¹⁹⁾ To be sure, that number has increased in the past eight years. The traditional relationship between NIH and Academic Health Centers (AHC), as repositories of such clinical research, is changing as increasingly clinical research is “managed” by Contract Research Organizations (CROs) and Site Management Organizations (SMOs) that are involved in the majority of subject recruitment for clinical research.

Due to this shift in clinical research funding sources, the vast majority of clinical trials are no longer regulated by the NIH as a funding source but ultimately by the Food and Drug Administration (FDA) through their biologics or medical device divisions and other agencies. A series of guidance documents issued by the FDA between 1989 and through the 1990s *encouraged* researchers to analyze clinical trial data to determine differences among subpopulations. In 1998 the “Final Rule on Investigational New Drug Applications and New Drug Applications (Demographic Rule) ultimately required that analyses of effectiveness and safety data for important demographic subgroups, including race, be included in New Drug Applications (NDAs) and that enrollment of subjects in clinical studies for drug and biological products be tabulated by important demographic subgroups in investigational new drug (IND) annual reports.⁽²⁰⁾ Thus, while these regulations require *analysis* of clinical trial participation by subgroup, they do not specifically require *inclusion* of subgroups as subjects. However, inconsistency in reporting such data led the FDA to publish a Guidance document or a “nonbinding initiative” in 2005 recommending that sponsors use the standardized approach developed by the Office of Management and Budget (OMB); an approach already adopted by all

HHS agencies. Notably, although one of the FDA’s desired outcomes of the 1998 regulation were to “help focus drug sponsor’s attention” to enrolling subjects in clinical trials who represented “the various subgroup of the population expected to use the drug being tested once it is approved and marketed,”⁽²¹⁾ this has not yet been achieved. A 2008 study found that participants in cardiovascular studies relied on by the Centers for Medicare and Medicaid (CMS) for coverage determinations differed substantially from the Medicare population.⁽²²⁾ In particular, the study participants generally represented younger, healthier, male, non-US populations while the target population for the cardiovascular medication was mostly older female with co-morbidity and exclusively from the United States.⁽²³⁾

Rettig raises the question of whether “existing organizations for ‘managing’ this enterprise is adequate from a policy standpoint?”⁽²⁴⁾ A similar question, with a more narrow focus is raised by this article. Specifically, whether the regulatory oversight of the NIH has been effective in assuring women and minorities are included in clinical trials. The answer to this query has two distinct parts. First, it appears that the regulatory requirements of the NIH Revitalization Act of 1993 for inclusion of women and minorities in clinical trials and the subsequent regulatory oversight by the NIH, has been effective in increasing the participation of these populations. However, the *relevance* of this agency in assuring overall inclusion of women and minorities has diminished with the increase of industry-sponsored clinical research. Second, if we assume that a legitimate policy initiative involves ethically and technically sound design of clinical research trials and the assurance of safety and efficacy of drugs for *all* populations, then we must focus on clinical trial oversight by the Food and Drug Administration. In doing so, we

can conclude that additional policy initiatives are necessary in order to achieve increased recruitment and retention of women and minorities in future clinical research.

Toward that end, in January 2009 the FDA issued a request for comments “seeking information to see if additional approaches are necessary to increase participation of certain subsets of the population”

and “best practice approaches in increasing participation.”⁽²⁵⁾ This recent movement toward policy refinements that are in alignment with several EDICT recommendations is a positive indication that arguments of social justice are being heard and are working their way through the maze of health policy toward eliminating disparities in clinical trial participation.

In a modern era of “personalized medicine,” clinical research should fill in the “gaps in knowledge” concerning diseases and health conditions that are disproportionately experienced by certain subpopulations and gender.

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