

Introduction

We, at the Eliminating Disparities in Clinical Trials (EDICT) Project, appreciate the opportunity to respond to the revised NCD and applaud CMS efforts to revisit the benefit issues related to clinical trials. The EDICT Project, launched in 2005, is a research study designed to address the problems and find workable solutions to recruiting and retaining populations that are underrepresented in clinical trials such as low income, elderly, racial-ethnic minorities or those who live in rural areas.

We greatly appreciate the fact that the proposed changes have engendered a productive dialogue from various stakeholders in distinct voices. Moreover, we understand the practical concerns that some organizations have noted in response to the proposed changes. Nevertheless, because we believe that the proposed changes enhance the quality of clinical research, facilitate the equal access that Medicare is designed to ensure, and improve returns on investment, we write in strong support of the proposed changes.

Much of the opposition to the proposed changes seems to center around several basic claims. First, there is a sentiment that the proposed changes are not needed since the NIH Revitalization Act requires and FDA guidelines recommend inclusion of underrepresented populations in clinical trials absent compelling nondiscriminatory exclusion criteria. Second, there is a concern that the self-certification process will increase burdens on institutions and research teams that conduct clinical research, potentially decreasing participation by Medicare beneficiaries and reversing the progress made since the last changes in the clinical trials policy in 2000. For several reasons, we do not share these positions.

Federal Initiatives Have Not Prevented Widespread Disparities in Clinical Trials

First, the NIH Revitalization Act applies only to federally funded trials. A 1999 GAO report cited a PhRMA official's estimate that 80% of all drug trials are funded by industry.¹ As such, the reach of the Revitalization Act is inherently limited. Richard Rettig noted in 2000 that "the entire clinical research enterprise is no longer anchored firmly in the public sector."² Moreover, the trend over the last twenty-five years has tilted toward greater private and lesser public sponsorship of trials, so it is reasonable to expect further retrenchment on the scope of the Revitalization Act.

Second, the methodology NIH uses to track the rates of underserved populations participating in clinical research measures only enrollment.³ This is important, because unless retention of research subjects is measured, there is simply no way to be sure what percentages of those who enroll are retained. The proportions of members of underserved populations who enroll in clinical trials is not evidence of the proportions of those members retained in clinical trials. A 2001 study, for example, found that subjects who tended to withdraw from the trial tended to be female and members of ethnic minorities, both of which constitute underrepresented populations in clinical trials.⁴ It is difficult to see how CMS can see a return on its investment in increasing access to

clinical trials unless attention is given to insure that members of underserved populations are retained in clinical trials.

Third, IRBs spend an overwhelming amount of their resources on initial review of protocols, with comparatively little attention devoted to continuing review. The applicable regulations require continuing reviews to be performed only once per year.⁵ The OIG's comprehensive 1998 report quotes one IRB member as reporting that "he reviews the continuing review summaries during the board meeting to see if a patient has died. If no patient has died, then he generally will not raise questions."⁶ Accordingly, even where IRBs scrutinize protocols to be sure they comply with the Revitalization Act, the IRB system is generally not equipped to evaluate protocols as they are conducted to ascertain whether participants who are members of underserved populations are retained.

Fourth, the FDA guidelines are just that – guidelines – and are not compulsory. Even with the requirements of the Revitalization Act, the evidence overwhelmingly demonstrates significant disparities in clinical trials, with the populations that bear the highest disease burdens tending to be dramatically underrepresented in clinical trials. A 2005 AHRQ report indicated that the elderly, those of low socioeconomic status, those living in rural areas, Latino/Hispanic, Asian/Pacific Islander, American Indian/Alaska native men and women, and African-American men are all underrepresented in cancer clinical trials.⁷ Similarly, a 2006 study in *Cancer* noted that more than a decade after the passage of the Revitalization Act, "certain populations are still underrepresented in cancer-related clinical trials, including racial and ethnic minorities, older adults, adolescents, rural populations, and individuals of low socioeconomic status (SES)."⁸ Even more recently, the *Annals of Surgical Oncology* has released a study online (published online August 8, 2007) which found that racial/ethnic minorities and elderly persons were less likely to enroll in clinical trials than Caucasians and younger persons.⁹

Thus, there is ample reason to believe that populations, such as the elderly,¹⁰ that bear disproportionate burdens of disease continue to be dramatically underrepresented in clinical trials. Ameliorating this trend has proved difficult, even with the Revitalization Act and the relevant FDA guidelines.

There is Little Reason to Believe the Proposed Changes Will Prove Impracticable

Two further points are worth mentioning as to the proposed changes regarding self-certification. As to the concerns that the proposed changes are too onerous, Steven Epstein's extremely recent and exhaustively researched book on the issue of including underserved populations in clinical research documents similar objections being raised to the Revitalization Act.¹¹ Fourteen years later, there are relatively few claims that the Act demonstrably slowed the pace of clinical research or rained down the parade of horrors its most vehement detractors predicted. There is abundant evidence suggesting that certain populations' underrepresentation in clinical trials remains a serious problem. In contrast, there is little evidence explaining why or how CMS's modest measures designed to address this problem as to Medicare beneficiaries will prove an impossible burden.

Ameliorating Disparities in Clinical Trials Enhances Research Quality, Social Justice, and Returns on Investment

Finally, ameliorating disparities in clinical trials simultaneously enhances the quality of the research, furthers social justice, and facilitates returns on R&D investment. Regarding research quality, a commitment to evidence-based medicine requires means of assessing what counts as good evidence. In many cases, the best evidence demonstrates that the intervention is generalizable across the entire patient population. In other cases, the best evidence demonstrates the effect of an intervention in a specific population (whether identified by race, ethnicity, gender, disability status, age, etc.).

However, in both cases, the evidence will be stronger if the widespread disparities in clinical trials are ameliorated. This is because a subject population that displays such disparities will not resemble the intended patient population, whether that population is the general public or a specific community. Therefore, reducing these disparities results in better scientific evidence, which can then be translated into better clinical practice, which will provide greater benefit to the public.

As to social justice, ameliorating disparities in clinical trials is consistent with ethical commitments to distribute the fruits of biomedical research justly.¹² Many of the underrepresented populations, including Hispanic/Latino women, African-American men, the elderly, children, and disabled persons, were victims of unethical research programs in the twentieth century. These same populations are among those that bear disproportionate burdens of disease. Tracking Plato's account of justice as giving each person their due, it is reasonable to conclude that justice demands that steps be taken to reduce the continuing disparities in clinical trials. There is no justification for the notion that members of underserved populations are due less benefits of clinical research than others, especially when such populations bear disproportionate burdens of disease and have been victims of unethical research. Ultimately, the proposed changes are an important component in giving each their due, and therefore reflect a deep commitment to social justice.

The reason why ameliorating disparities in clinical trials will promote returns on R&D investment is because results from trials featuring proportionate representation constitute better evidence. As a result, sponsors of interventions can justifiably claim that an intervention that has proved efficacious in a clinical trial that featured proportionate representation is better suited for integration into existing practice guidelines than an intervention arising from a trial that lacked proportionality. In short, ameliorating disparities in clinical trials may provide sponsors an advantage in positioning their products in the stream of commerce.

Conclusion

In conclusion, we again wish to express gratitude to all the stakeholders who have engaged in dialogue on such an important issue. While change is not always easy, it is all-too-often needed, and the proposed changes to the clinical trials policy are responsive

to this need. Despite the best intentions of policymakers and stakeholders, the evidence conclusively shows that there remain widespread disparities across the clinical research enterprise. Fears of insurance coverage and reimbursement are a well-known barrier to participation in clinical research,¹³ and the proposed changes to the clinical trials policy are a crucial step towards ameliorating this barrier in particular. Thus, the proposed changes are needed to ensure that the medically underserved populations that bear disproportionate burdens of disease are treated justly in sharing in the fruits of clinical research.

Sincerely,

Armin D. Weinberg, PhD
Principal Investigator
EDICT (Eliminating Disparities in Clinical Trials) Project
Chronic Disease Prevention and Control Research Center
Baylor College of Medicine
Houston, Texas

¹ See General Accounting Office, NIH Clinical Trials: Various Factors Affect Patient Participation 1, 4 (1999), available at <http://www.gao.gov/archive/1999/he99182.pdf> (last accessed August 18, 2007); see also Hamilton Moses III, E. Ray Dorsey, David H. Matheson, and Samuel O. Thier, *Financial Anatomy of Biomedical Research*, 294 JAMA 1333, 1335 (2005).

² Richard Rettig, *The Industrialization of Clinical Research*, 19 HEALTH AFFAIRS 129, 140 (2000).

³ See Department of Health and Human Services, National Institutes of Health, *Monitoring Adherence to the NIH Policy on the Inclusion of Women and Minorities as Subjects in Clinical Research: Comprehensive Report Tracking Human Subjects Research as Reported in Fiscal Year 2005 and Fiscal Year 2006*, available at <http://orwh.od.nih.gov/inclusion/2007acr-5-2-07.pdf> (last accessed August 17, 2007).

⁴ See Susan L. Janson, Maria Elena Alioto, and Homer A. Boushey, *Attrition and Retention of Ethnically Diverse Subjects in a Multicenter Randomized Controlled Research Trial*, 22 CONTROLLED CLINICAL TRIALS 236S, 238S-239S (2001).

⁵ 45 C.F.R. § 46.109 (2007).

⁶ Department of Health & Human Services, Office of Inspector General, *Institutional Review Boards: A Time for Reform* 1, 6 (1998), available at <http://oig.hhs.gov/oei/reports/oei-01-97-00193.pdf> (last accessed August 17, 2007). Since OIG's report, there is little evidence that significant progress has been made in improving the continuing review process. Indeed, the OIG's 2000 follow-up report expressly noted that few of its recommended reforms had been enacted, and minimal progress had been made. See Department of Health & Human Services, Office of Inspector General, *Protecting Subjects: Status of Recommendations* 1, 2 (2000), available at <http://oig.hhs.gov/oei/reports/oei-01-97-00197.pdf> (last accessed August 17, 2007).

⁷ J.G. Ford et al., *Knowledge and Access to Information on Recruitment of Underrepresented Populations to Cancer Clinical Trials*, 122 AHRQ EVIDENCE REP./TECH. ASSESSMENT 1, 1 (2005).

⁸ Shari Bolen et al., *Defining "Success" In Recruitment of Underrepresented Populations to Cancer Clinical Trials: Moving Towards a More Consistent Approach*, 106 CANCER 1197, 1998 (2006).

⁹ See John H. Stewart et al., *Participation in Surgical Oncology Clinical Trials: Gender-, Race/Ethnicity-, and Age-based Disparities*, ANN. SURG. ONCOLOGY, available at <http://www.springerlink.com/content/wr832v6285x154j1/?p=14c72fd1525748dea4925a36cc38c5e8&pi=8> (last accessed August 18, 2007).

¹⁰ See Intercultural Cancer Council Network, *Cancer Clinical Trials: Participation by Underrepresented Populations*, available at <http://www.iccnetwork.org/cancerfacts/cfs11.htm> (last accessed August 18, 2007).

¹¹ Steven Epstein, INCLUSION: THE POLITICS OF DIFFERENCE IN MEDICAL RESEARCH 103-106 (2007).

¹² See, e.g., Dorothy E. Roberts, *Legal Constraints On the Use of Race in Biomedical Research: Toward a Social Justice Framework*, 34 J. L. MED. & ETHICS 526 (2006); Barbara Noah, *The Participation of Underrepresented Minorities in Clinical Research*, 29 AM. J. L. & MED. 221 (2003).

¹³ See Primo N. Lara, et al., *Prospective Evaluation of Cancer Clinical Trial Accrual Patterns: Identifying Potential Barriers to Enrollment*, 19 J. CLIN. ONCOLOGY 1728, 1732 (2001); Robert Finn, *Surveys Identify Barriers to Participation in Clinical Trials*, 92 J. NAT. CANCER INST. 1556, 1557 (2000).