Barriers to Medically Underserved Peoples Participation and Retention in Clinical Trials

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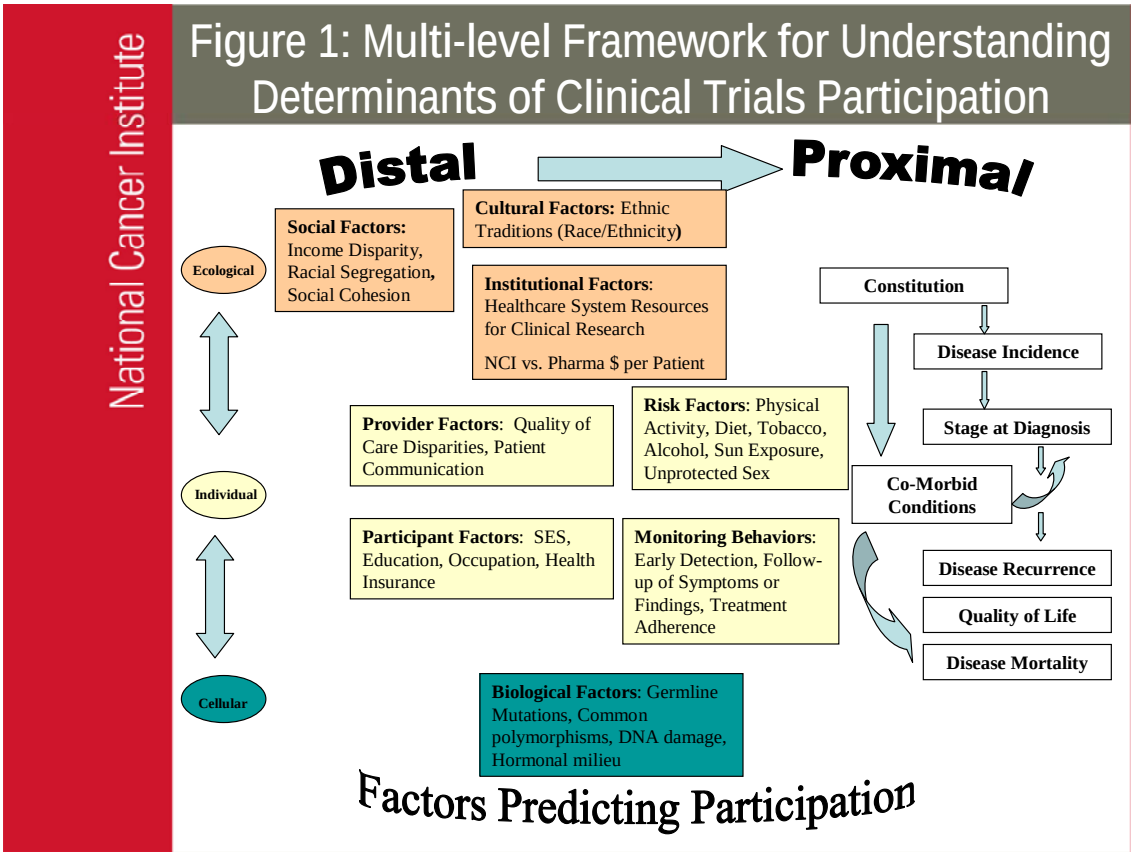
How should we think about the barriers?

Understanding how to eliminate disparities in clinical trials requires a recognition that the barriers operate on more than an individual patient or practitioner level. As Figure 1 suggests



ecological factors and biological factors need to be considered if we are to eliminate these disparities now and in the future. Even at the individual level, the complexity of the processes that deter or promote clinical trials participation need to be recognized. For example, differences in risk-factor and illness monitoring behaviors contribute to a higher prevalence of co-morbid illness and later stage-of-disease at diagnosis among some medically underserved populations, and this will impact for which protocols different populations may be more or less likely eligible.

In June 2005 NCI commissioned and supported through the AHRQ-Evidence Practice Center at Johns Hopkins University a systematic evidence review report entitled: *Knowledge and Access to Information on Recruitment of Underrepresented Populations to Cancer Clinical Trials* (http://cancercontrol.cancer.gov/d4d/evidence_report/recruit_7-7.pdf). The majority of the studies reviewed addressed barriers to, versus promoters of, clinical trials participation. For barrier and promoter studies, the overwhelming majority focused on patient and provider issues. Only seven published studies reviewed addressed system level barriers (e.g., access to institutions conducting clinical trials) and only two studies addressed system level promoters (e.g., patient and provider incentives).

In brief, the review found that there are:

- More barriers to opportunity than to awareness or acceptance
- More evidence on barriers than on promoters
- Mistrust a common theme
- Provider barriers exist at level of professionals, study design & healthcare system
- Sparse evidence on efficacy of recruitment strategies (5 studies)
- Recruitment goals are rarely reported *a priori* (2 studies)
- Variety of methods are used to study recruitment

In brief, the review recommended that the research enterprise should:

- Report
  - *a priori* recruitment goals & results
- Consider
  - conceptual framework in design & evaluation of recruitment strategies
- Train investigators
- Evaluate
  - Role of underrepresented healthcare professionals & community health workers
  - Cost-effectiveness of interventions
  - Tailored & targeted recruitment interventions

While this report helps point the way for how randomized clinical trials (RCT) research in general can more systematically incorporate minority and medically underserved population accrual goals into study designs, and should include rigorous evaluations of the successes and failures of these recruitment efforts, other systems level and policy questions that should also be considered are who funds what research and to what end?

Where do and should government, industrial, and academic sectors focus funding?

At the 2006 meeting of the American Society of Clinical Oncology, the President's Cancer Panel presentation reviewed the challenges of translational research and research translation. In the 2005-2006 written report (http://deainfo.nci.nih.gov/advisory/pcp/pcp.htm) distributed at the meeting several relevant points were noted:

> ...we face a continued decline in reimbursement....we are constantly fighting that battle so that clinical research programs can stay alive, because the patients are...staying in the community.
>
> – *Community oncologist*

Of equal concern, as older cancer drugs (e.g., cisplatin) that are the mainstay of many current treatments lose patent protection and their profitability, some pharmaceutical companies are electing to cease production of these essential agents, potentially leading to short supplies of life-saving medications. The Panel reiterates its contention that to encourage new cancer drug development and ensure adequate supplies of mainstay treatments, cancer should be designated an orphan disease,[4] thereby enabling drug developers and manufacturers to obtain support to offset specific elements of cost and extend patent protection for approved agents.

- Disincentive for investment in less common diseases or risky, innovative approaches
- Rapidly escalating costs & complexity decrease willingness and ability to bring many candidates forward into the clinic

The myriad ramifications of scarce funding for critical cancer research and cancer care activities are cause for urgent concern. Even if these problems are addressed, all stakeholders involved in cancer research and cancer care must seek out and seize every opportunity to work collaboratively and efficiently to make the most of available resources.

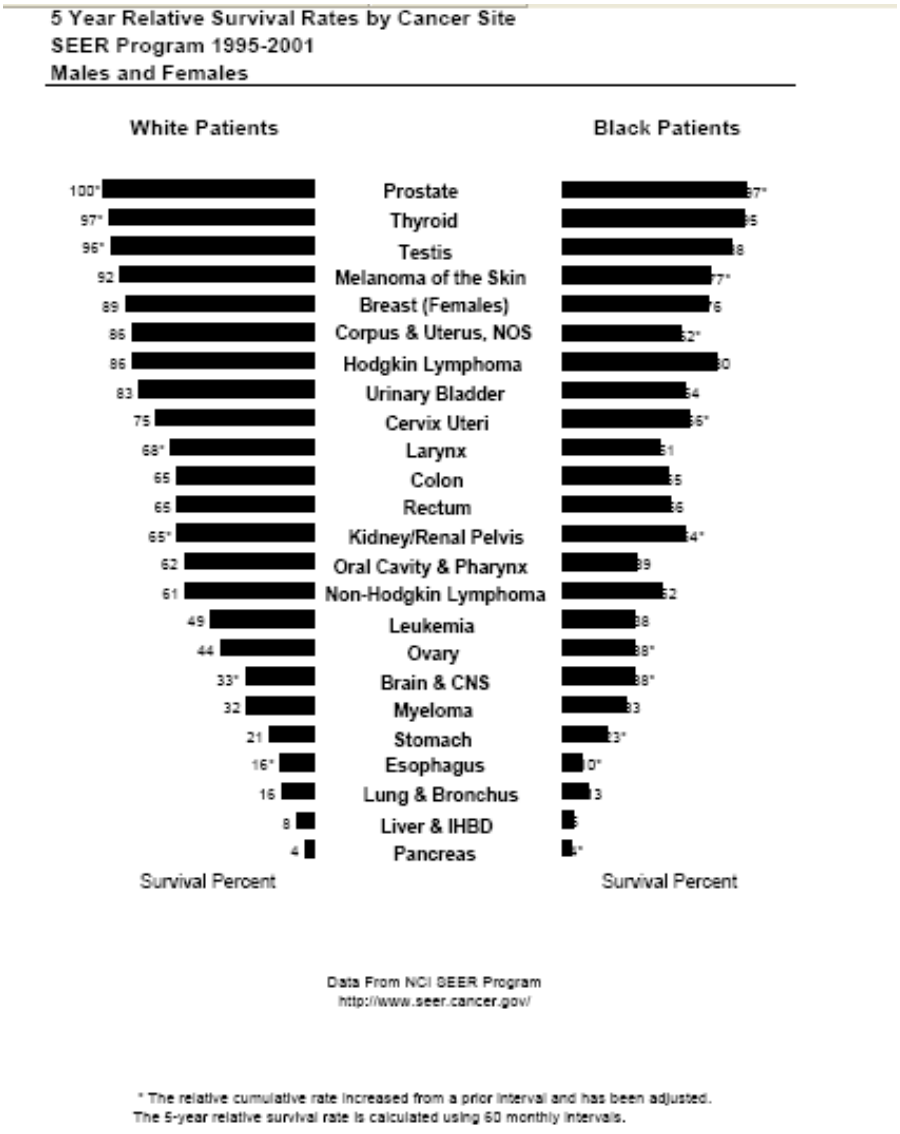
Given that 57% of all clinical trials are funded by industry and less than 30% are funded by NIH (R. Padzur (FDA), personal communication), and given that only 16.3% of the NCI's FY05 budget (2005 Cancer Fact Book - http://fmb.cancer.gov/financial/Factbook.htm) was devoted to clinical trials research, the question arises does the funding of cancer clinical trials research impact who gets into studies and who does not?

If industry were to understandably be focused on investing in the development of new treatment interventions where the incidence burden is greatest for all populations (e.g., lung, colorectal, prostate and breast cancers), there would be little financial incentive for industry to focus on cancers where overall incidence was relatively low even if the relative incidence and mortality was quite high for minority and other medically underserved populations.

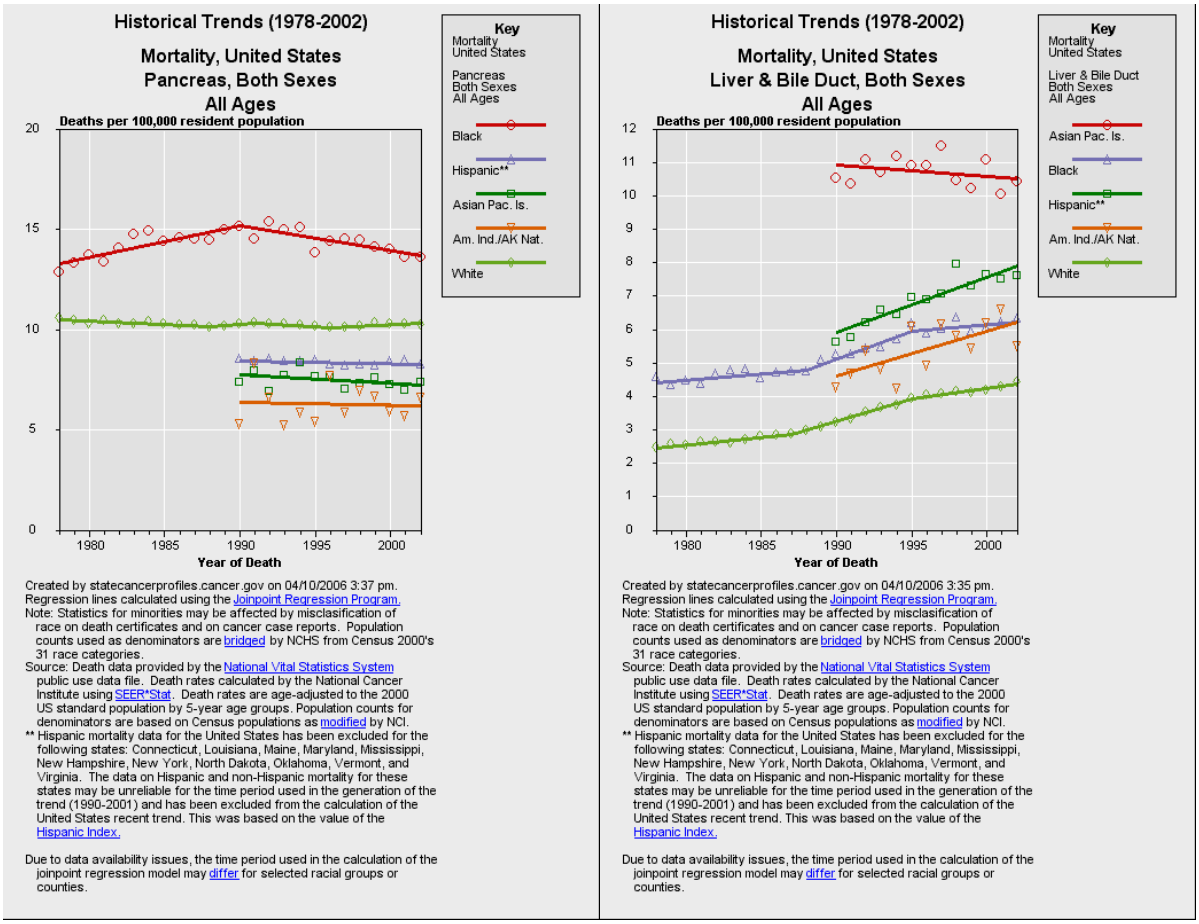
Which diseases might we focus on?

If this were the case in terms of industry priorities, might we ask should government's more limited investment in clinical research be focused on other priority populations? For example,

should NCI's investment focus more on those cancers where, irrespective of the overall incidence burden, cancer case fatality rates are uniformly high (e.g., pancreas, liver) and/or the relative incidence/mortality burden is particularly high for medically underserved populations? Using pancreas and liver only as examples, we can see from the figure below that pancreas and liver cancers have the lowest 5-year relative survival rates for both white and black patients.

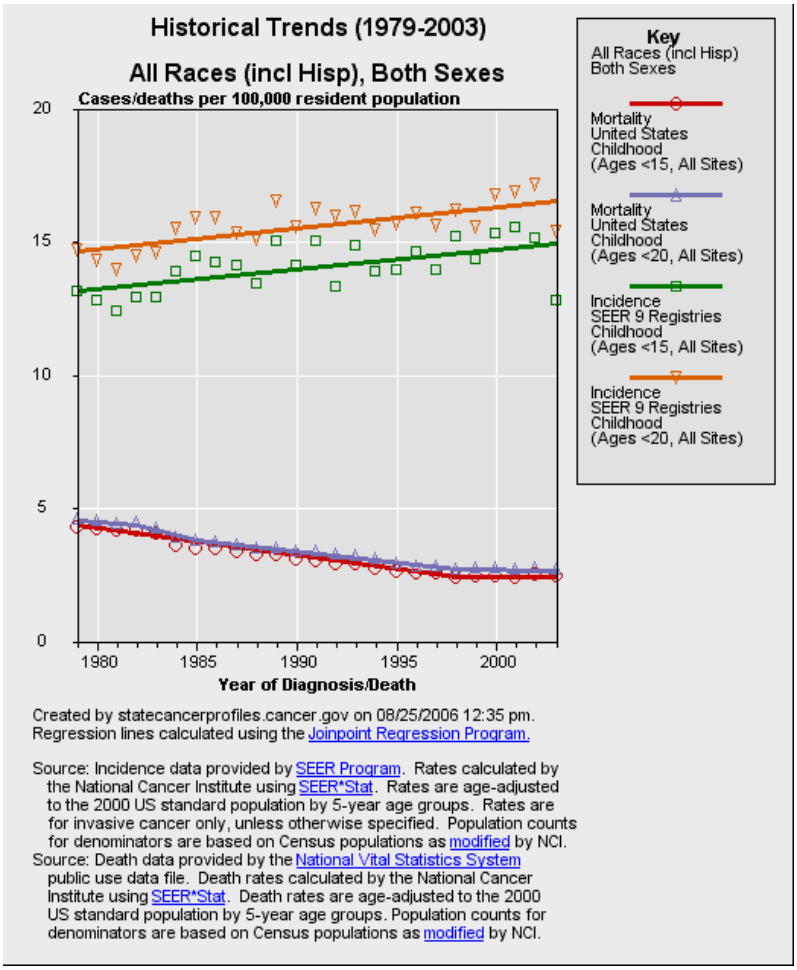


Thus, for pancreatic cancer there were an estimated 32,180 new cancer cases in the U.S. and an estimated 31,800 deaths in 2005. Similarly, there were an estimated 17,550 new cases of, and an estimated 15,420 deaths from, liver and intrahepatic bile duct cancer in the U.S. This almost one to one ratio of deaths to new cases diagnosed reflects how little progress has been made to address these important but not as highly prevalent cancer killers. Moreover, there are marked differences in risk for both these diseases among minority and medically underserved populations (see figure below). Thus, high case fatality rates and differential population burden could be factors that help focus our cancer research investment policy.



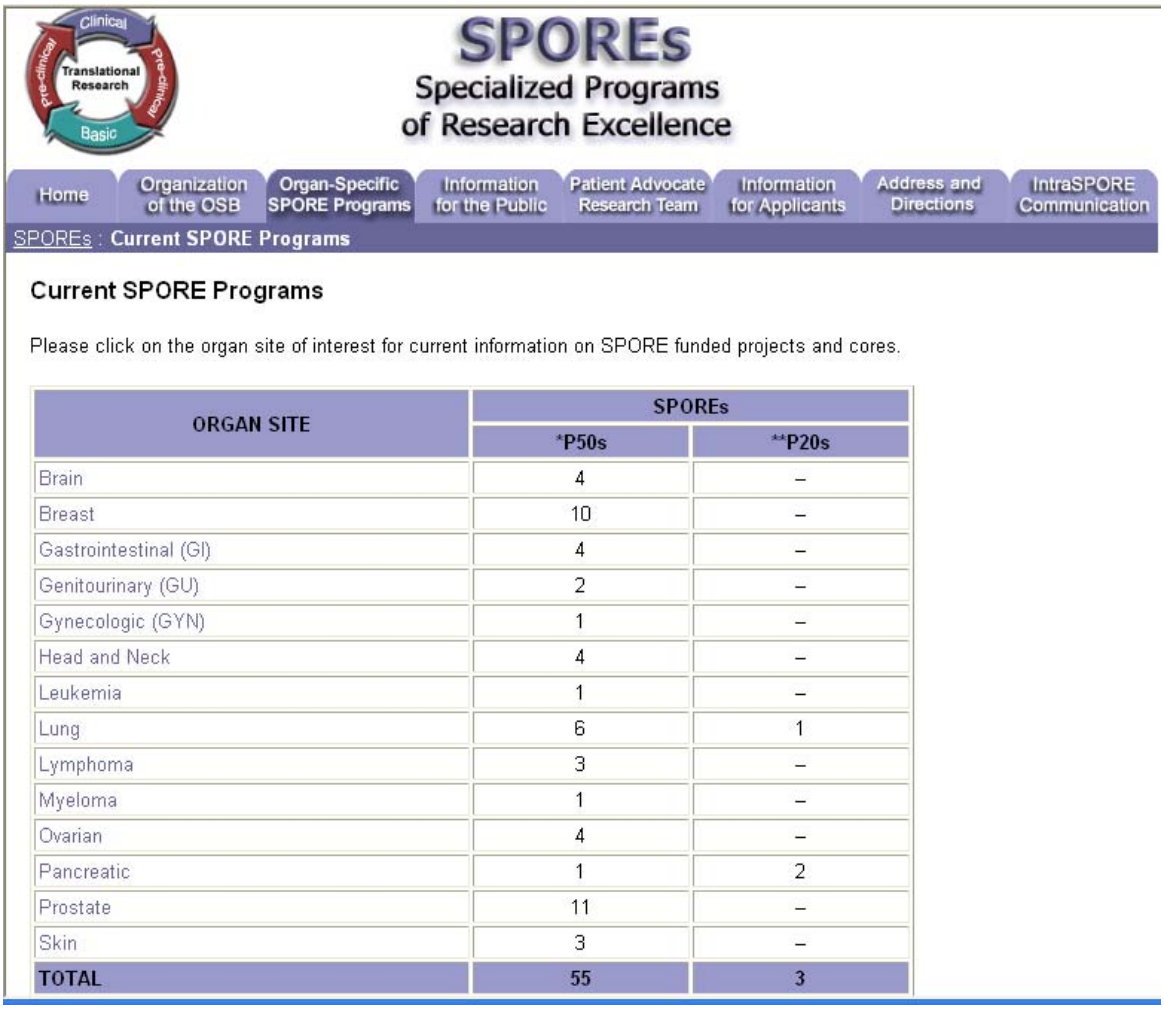
Looking back into history, we have an outstanding example of where a focused approach to research led to a significant difference in cancer outcomes: Pediatric cancer clinical research. Thus, as the figure below indicates, when government, academia and industry got together in the 1970's they came up with a cooperative and collaborative model for insuring that upwards of 90% of all pediatric cancer patients were entered onto clinical trials. The return on this focused approach and research investment led to high clinical trials participation, albeit within a limited number of clinical research settings, rapid improvements in pediatric cancer care, and steady reductions in cancer mortality over time even as the incidence rates were on the rise.

Could a similar approach on a focused set of adult cancers, with comparably low incidence and high case fatality rates, lead to similar progress? What system factors differentiate the management of pediatric cancer from the management of high case fatality adult cancers like pancreas and liver cancer, and how would these differences impact the likelihood of achieving 80-90% participation rates in clinical trials for these rarer adult cancer cancers? If such high clinical trials participation rates could be achieved for selected adult cancer sites, it would per force eliminate the disparities in clinical trials participation and perhaps improve the attitude of many underserved communities to the benefits of participating in clinical research.



So what has been NCI's relative investment in the development and testing of new interventions to address these two cancers? While it is difficult to separate out basic science, clinical research and population science NCI investments for any cancer, one surrogate measure of NCI's relative investment in site-specific clinical research is the number of Special Programs of Research Excellence (SPOREs) funded by cancer site. SPOREs are funded through specialized center grants (P50s) that promote interdisciplinary research and move basic research findings from the laboratory to clinical settings, involving both cancer patients and populations at risk of cancer.

As the table below indicates, of the 55 fully funded SPORE Center grants, only one is focused on pancreatic cancer and there are no SPOREs focused on liver cancer. Is the state of the science such that we know so little that it is premature to be investing in translational research, or rather is our understanding of the etiology and mechanisms of these cancers today similar to what we knew about pediatric cancers in the 1970's, and thus the explanation for not making such a targeted investment approach lies elsewhere? Does the relative dearth of many vocal advocacy organizations for these lethal adult cancers contribute to the relative lack of investment? Should the differential burden of among medically underserved populations, combined with the uniformly poor outcomes post-diagnosis, change our funding priorities? What are the roles of academic centers in not building programs and seeking more funding for these "orphan" cancer killers, and does this reinforce the spread of our limited resources a mile wide and an inch deep?



ORGAN SITE	SPOREs	
	*P50s	**P20s
Brain	4	–
Breast	10	–
Gastrointestinal (GI)	4	–
Genitourinary (GU)	2	–
Gynecologic (GYN)	1	–
Head and Neck	4	–
Leukemia	1	–
Lung	6	1
Lymphoma	3	–
Myeloma	1	–
Ovarian	4	–
Pancreatic	1	2
Prostate	11	–
Skin	3	–
TOTAL	55	3

Summary

As we pursue the discussion of how best to identify policies that can help to eliminate disparities in clinical trials, the cancer experience provides some questions that may prove useful in trying to sort out policy solutions to this long standing challenge across many chronic diseases.

1) Are we considering all levels of barriers, beyond the patient and the provider?
2) Will the movement towards more personalized medicine exacerbate the problem of disparities, based on the expense of individually tailored regimens based on biology?
3) How do research funding priorities of government and industry influence which populations benefit from participating in clinical research?
4) What forces influence these funding priorities, and is it reasonable that government and industry would have different but complementary research investment foci?
5) Can a more targeted investment and coordinated clinical trials participation approach lead to a much higher overall participation in clinical trials and thus eliminate disparities?
6) Can the healthcare system accommodate focused accrual to clinical trials in centers of excellence and maintain high quality, community-based conventional care?
7) Do we have the "political" will to find the policy way to overcome these challenges?