The "Three R's" of Clinical Trial Participation: An Organizing Framework. *By Dan Bustillos JD, PhD (cand.)*

The arguments that compel a more equitable inclusion of participants into clinical trials are hardly controversial or unknown. For example, there is no longer any doubt that both genetic and non-genetic factors can cause large differences in how certain groups of individuals react, metabolize, and are affected by the same drug.[1] Thus, if for no other reason than for the safety of prospective consumers, drug trials should include as diverse a sample of volunteers as possible. This compelling reason, along with equally persuasive distributive justice arguments, have played a great part in the recent emphasis on the "inclusiveness" that should pervade clinical trials. Women, "racial and ethnic minorities", children, prisoners, etc., have all been the object of eloquent and persuasive calls for more inclusive clinical trials. Laws and agency regulations require that marginalized populations be included, especially into trials wherein lies hope for direct benefit to the participant. Nonetheless, the majority of clinical trials continue to display a depressing homogeneity in their subject populations—largely, married, white males. This is compounded by the fact that patients from medically underserved populations (e.g., African Americans, Latinos, rural, poor) bear a disproportionate burden of cancer death but the smallest percentage of clinical trial participation.[2] The Eliminating Disparities in Clinical Trials ("EDICT") project headed up by Baylor College of Medicine's Chronic Disease Prevention and Research Center and the Intercultural Cancer Council is designed to culminate in practicable and implementable policy and operational solutions to this problem.[3] As such, an organizational framework to help orient our policy investigation and discussion was developed by the EDICT project.

The Three R's: Recruitment, Retention, and Return

For too long, the clinical trials enterprise has lacked a holistic framework for addressing questions of policy. As Dr. McGuire notes in her EDICT article: "it is essential that current and future policy development be grounded in a coherent conceptual model that defines and distinguishes the various phases of research, including recruitment, informed consent, enrollment, participation, and post-trial treatment and follow-up care."[4] In the existing policy literature, the vast majority of studies focus on the recruitment of individuals or the ethics of human subjects research. Relatively little attention has been paid to the retention of patients in clinical trials that may pose a direct benefit, and next to nothing has been written about whether researchers or sponsors have a duty to "give something back" to the participants and their communities after the study concludes.[5]

For this reason, we introduce an organizing framework that will serve to orient our discussion at the September 2006 EDICT meeting in Houston as well as serve as a broader framework for the entire 4-year EDICT project. We feel confident that it will also serve as a useful heuristic for the broader policy discussion about equity in human subjects research.

Recruitment

Threshold questions

As might be expected, the first "R" of clinical trial participation is recruitment. Most studies dealing with issues of equity and ethics of clinical trial participation focus on the issue of recruitment of subjects. Many articles have been written about the importance of recruiting diverse populations, the various barriers that complicate an equitable selection of participants, the ethics of recruiting, strategies for a more inclusive participant population, etc.. These reports are important and necessary as the recruitment stage is of course crucial to broader questions of justice and parity in clinical trials. However, we should look at each of the three R's more holistically both within themselves and in relation to the other R's. Thus, when identifying specific operational changes or policies to address problems of recruitment disparities in clinical trials, we should start with threshold questions upon which the more obvious problems might be predicated. First, we should ask whether the panoply of clinical trials available adequately addresses the relevant health problems of medically-underserved populations. As has been widely noted, economic rationales, researcher and sponsor apathy and ignorance as to the plight of marginalized populations, and possibly even racist motives can be responsible for the inability of getting certain "minority health" trials funded, and for the general unavailability of relevant trials for minorities and the medically underserved.[6]

As such, the first "R" must be considered a broader concept than mere strategies for more inclusive recruitment. We must be concerned with raising awareness among researchers, clinical trial sponsors, and the public on the necessity of designing and funding studies that serve the interests of populations whose voices may not be heard over the din of economic prospecting.

Being thoughtful about the kinds of clinical trials that the underserved population need or are clamoring for will go a long way towards proactively solving the problem of inadequate accrual.

In addition, many clinical trials are designed with overly strict exclusion criteria that tend to discriminate against certain population groups. For example, most clinical trial designers unreflectively place boilerplate language excluding candidate participants with "comorbidities", those that speak languages other than English, or potential subjects over a certain age. While it may be scientifically necessary to exclude certain patients with other confounding illnesses and conditions, is it strictly necessary to summarily exclude so many? Are obesity, poverty, the ability to speak more than one language, or lack of access to certain resources legitimate reasons to close a trial to a candidate participant? Answers to these policy questions should be arrived at by frank discussion by members of all the sectors involved in the clinical trials enterprise including private industry, government, philanthropy, and advocacy.

After we tackle the threshold question of whether and how clinical trials are addressing the needs of the underserved, it then becomes appropriate to turn our attention to the practical barriers that patients face when considering whether to participate in a potentially beneficial clinical trial. These barriers are not insurmountable if properly and adequately addressed by the researcher or clinical trial sponsor. One solution to the barrier problem is to consider potential issues at the design stage. If a socially, economically, and genotypically diverse subject population is needed to ensure the safety, efficacy, and equity of approved drugs, devices and interventions, then doesn't it make sense that adequately providing for "barrier-busting" within the study budget is absolutely essential? Today, too many trials fail to pay appropriate attention to questions of culture, language, and poverty at the stage of study design, making post-hoc adjustments to the protocol necessary to get an equitable selection of participants. Unfortunately, waiting until the recruitment stage is underway to start thinking of equitable accrual results in efforts that are too little, too late, and much more difficult to fund adequately.

In a detailed literature review done last year, the Agency for Healthcare Research and Quality (AHRQ) indicated that more research needs to be done to identify which recruitment interventions are the most successful at improving recruitment outcome. "There is only scant evidence in support of specific interventions to improve recruitment to cancer clinical trials, as indicated by the small number of studies comparing interventions."[7] The report goes on to state that there is little or no data on recruitment barriers and/or promoters in certain disadvantaged groups. Any comprehensive policy strategy must place an emphasis on studying the efficacy of promoters to clinical trials and of barrier elimination.

Table 1. The recent AHRQ literature review listed many different barriers to recruitment into cancer clinical trials as well as proven promoters. Here are some of the most important.

Barriers	Promoters
• Barriers to awareness • Barriers to opportunity • Barriers to acceptance • Misconceptions as to the nature/risk of research • Fear • Mistrust • Disease stage • Lack of trial availability in geographic location • Lack of trial availability for patient's particular disease • Inconsistent IRB standards • Poor study design • Lack of insurance (trial expenses not covered by insurance) • Cultural/religious qualms about research • Lack of primary care provider's awareness of trials	• Culturally competent investigators • Culturally appropriate materials • Competent translation/interpretation services • Providing for transportation of participants • Reimbursement of study-related expenses • Payment and/or incentives • Altruism • Perceived benefits of participation • Advertising, media-based recruitment • Lack of insurance (trials that cover medical expenses seen as only means of health care) • Perception that it is better to be treated by research doctors • Regulatory agency guidelines

Retention

Certain underserved populations tend to drop out of clinical trial participation at a higher frequency than majority populations. While this continues to be a large problem on most research fronts, relatively little has been published to investigate the problem and offer solutions. Even less has been done to monitor the retention success of clinical trials with an eye to finding interventions that work in keeping participants in the study. The unexpected drop-out of patients is a costly problem and a symptom of the failure to design and operate clinical trials in ways that adequately address some of the problems we mentioned in the previous section.

We must attempt to look at the problem of retention during the research project in a manner that will yield proactive strategies rather than reactive stop-gap measures. Some important questions that we should ask ourselves are whether the clinical trial enterprise has the necessary infrastructures in place to provide an appealing, safe, and un-cumbersome experience for the participant without being unduly coercive. If culturally-competent researchers and nurses were able to administer clinical trials that were truly beneficial and relevant to the participant where some of the major hurdles of participating (e.g.: child-care, lodging, and trans-portation) were provided for, then retention would be drastically improved.

Return

The area of the clinical trials enterprise that gets the least attention is the post-trial period. What level of duty, if any, do researchers, sponsors, pharmaceutical companies, etc., owe the people whose self-sacrifice allowed for the private, intellectual, and societal benefits that are reaped from clinical trials? Should the populations that helped test new therapies have access to these after the trial is over? Should those who reap the financial rewards from others' sacrifice "give something back" to those participants and their communities? In the international clinical trial context, the Council for International Organizations of Medical Sciences ("CIOMS") has instituted guidelines for the

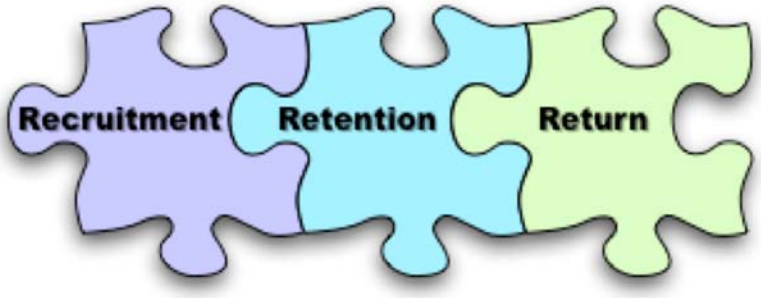
ethical conduct of clinical trials overseas. Among these guidelines are mandates that not only should foreign investigators assure access to the approved drug or therapy to participants after the trial has ended, but that communities that are "mined" for precious biospecimens should receive tangible, community-wide benefit post-trial.[8]

The post-trial benefits need not be costly to be valuable to the participant or their community. For example, clinical trials results and incidental findings can be of great value to participant populations that may then be in a much better position to guard their future health, push for needed interventions or research, modify health habits, in short—take fuller control of their wellbeing.

As for a potential return for the investigator or sponsor, aside from the obvious economic and intellectual benefits reaped, a continuing commitment to, and relationship with the participant population will have the added benefit of making subsequent attempts to enroll subjects from this community much easier than for a researcher who is perceived as being nothing more than a "bio-prospector."

Conclusion

The clinical trials enterprise is a complex and multi-faceted constellation of endeavors from many different sectors with many different agendas. This presents obvious difficulties when developing policies to achieve the ends of eliminating disparities in clinical trials. This is why a conceptual framework is necessary for the policymaker that takes into account the complexities and different phases of medical research. Utilizing the "Three R" framework can help root the policy discussion to specific phases with conceptually different problems. This will allow us to more precisely tailor policy strategies to achieve the results needed. ●



References

1. See Dr. Charles Rotimi's companion article "Understanding and Using Human Genetic Variation Knowledge in the Design and Conduct of Biomedical Research" in the EDICT Reading Room website: http://chronic.bcm.tmc.edu/edict/readingroom.html
2. Christian MC, Trimble EL. (2003) "Increasing Participation of Physicians and Patients from Underrepresented Racial and Ethnic Groups in National Cancer Institute-Sponsored Clinical Trials," Cancer Epidemiology, Biomarkers & Prevention, 12(3)., Giuliano AR, *et al.* (2000) "Participation of Minorities in Cancer Research: The Influence of Structural, Cultural, and Linguistic Factors" Annals of Epidemiology 10(8).
3. See EDICT website at http://chronic.bcm.edu/edict
4. See http://chronic.bcm.tmc.edu/edict/readingroom.html
5. Continued benefit to participants and their communities *has* been the object of much discussion and policymaking in the context of international clinical trials. See e.g.: Dr. Nick Iammarino's EDICT article at: http://chronic.bcm.tmc.edu/edict/International_Research.pdf
6. See generally, Haynes, M.A. and B.D. Smedley, eds. *The Unequal Burden of Cancer: An Assessment of NIH Research and Programs for Ethnic Minorites and the Medically Underserved.* 1999, National Academy Press, Washington, D.C.
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