


Diversity and Inclusiveness Should Remain the Guiding Principles for Clinical Trials

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The design of randomized controlled trials relies on theoretical principles that are at the core of clinical science. If performed successfully, randomization is assumed to provide a bias-free comparison of 2 or more groups that have the same prognosis. The difference between what did happen with treatment and what would have happened without it is therefore a rigorous test of efficacy and safety. Because we are almost never interested in interpreting this result within the narrow conditions of the trial, it is further assumed that the results of the trial are generalizable to the broader universe of study-eligible patients.

Most trials must therefore attempt to achieve 2 competing goals. First, the treatment must be submitted to a sufficiently rigorous test to determine whether it actually works. The second competing requirement is the need to determine the value of the intervention in routine practice. The first goal is generally best met by recruiting a narrow spectrum of patients who are most likely to benefit, often defined as the high-risk subset. These patients are selected because their high event rates will increase statistical power, not because their response will be unique or categorically different. The second condition can be addressed most effectively in large, simple studies that have few exclusion criteria and enroll patients from a wide range of settings. To mediate the tension between these opposing aims, it is almost always assumed that although the recruitment of high-risk patients may improve power, the treatment is unlikely to be associated with effect

modification, which would undermine the basis for generalizing to a broader group of patients.

Ethnic-specific trials, which in the United States included largely middle-aged white men, were once the norm. This approach did in fact generate concerns that age, sex, or ethnicity might modify the effects of treatment, and the preferred standard is currently to include diverse groups of patients in adequate sample sizes to explicitly test for differential response. The Antihypertensive and Lipid-Lowering to Prevent Heart Attack Trial (ALLHAT) is the most prominent example of a trial based on this principle.¹

At this time, ethnic-specific trials would seem to represent a step backwards. At the very least, they need to be supported by a theoretical rationale that can be integrated into the established framework for trials. This rationale could rest on the knowledge that the difference in intrinsic responsiveness is so large that the main effect would be diluted in a trial with a diverse sample of patients. This approach is analogous to the goal of choosing high-risk patients. Typically, a large number of epidemiological studies will have identified high-risk groups. The evidence supporting a differential effect of treatment across ethnic groups, on the other hand, is likely to be meager. A separate rationale for an ethnic approach to restriction would arise if prior clinical trials had shown a response present in only 1 group that could not be explained by known clinical factors or genetic variation. This result implies effect modification and, as suggested, would have

complicated the interpretation of the results of the original trial.

Although some overlap therefore exists between the “high-risk” and “ethnic-specific” design, there are also important potential differences. Because ethnicity is a categorical distinction, the basis for generalizing to other groups might be hard to establish. Selection of high-risk patients on the basis of clinical criteria usually supports a generalization to high-risk members of other ethnic groups, and milder cases, or it can provide direction for additional trials. After a positive trial in 1 ethnic group, it would be hard to judge whether the observed response is the same, better, or worse than would be expected in other groups or whether it is categorically different. This result occurs because the criterion for entry (ie, ethnicity) is not defined in clinical terms and does not provide any context for a judgment about generalizability to patients outside that category.

Although the implications of ethnic-specific trials are potentially quite broad, we focus on drug treatment for cardiovascular conditions among European- and African-origin populations in the United States, as reflected in a Food and Drug Administration (FDA) document on collection of ethnicity data and the African-American Heart Failure Trial (A-HeFT), a recently completed vasodilator trial.^{2,3} Given its obvious relevance to this debate and its importance as a potential test of the underlying principles, we will address the specific implications of AHeFT at the end of this discussion.

What Is Ethnicity?

Ethnicity is a catch-all term that describes a set of lifestyle/behavioral/cultural experiences. In racially stratified societies, culture, genes, and environment are strongly confounded.⁴ In practice, the term “ethnicity” often functions as a stand-in for race and refers to both potential genetic factors and acquired effects of environmental exposures. Although the term may remain indifferent about whether genetic and environmental effects are causal, its lack of clarity about which of the explanations is primary often leads to confusion. Because ethnic-specific trials assume that some inherent factor in the patient influences the response, interpretation would be easier if that factor were defined, and the results could be more easily generalized to other subgroups that shared that factor. When possible, therefore, the rationale for an ethnic-specific trial should be supported by arguments that distinguish between genetic or environmental effects. Otherwise, restriction of enrollment using such a “fuzzy” category could be an unreliable tool in clinical trials.

Do Major Cardiovascular Syndromes Vary Qualitatively, Rather Than Quantitatively, by Ethnicity?

The most obvious rationale for testing drugs in a single ethnicity is the idea that the pathophysiology of the disease is special or different in that group. This line of thinking clearly applies to cardiovascular disease in blacks, and an enormous

body of literature exists on this subject. Historically, for example, blacks are said to be stroke-prone but relatively protected from coronary heart disease.⁵ More frequent and more severe hypertension is the primary determinant of the black-white contrasts in clinical manifestations of cardiovascular diseases, and an extensive list of putative physiological and biochemical racial differences has been reported.^{6,7}

Two general conclusions have been advanced about this literature. Some observers are impressed by the nature of the differences and conclude that the manifestations of cardiovascular disease are unique among blacks. Others view these contrasts as epiphenomena that result from differential exposure to cardiovascular risk factors, themselves the consequence of different lifestyle patterns. This controversy cannot be resolved on the basis of current knowledge. We share the view that the clinically relevant racial differences are attributable largely to the degree or intensity of the environmental exposures, an interpretation often supported by epidemiological data. For example, trends over time demonstrate a relative increase in coronary disease among blacks in the last 50 years, and other European populations actually experience more hypertension and associated sequelae than do US blacks.^{8,9} Many of the “race-specific” effects, such as an increased prevalence of low-renin hypertension, are also seen in comparisons that stratify by level of risk within ethnicity, eg, age and gender, whereas many others are simply biochemical curiosities, such as differences in ion transport, with no known causal significance.^{6,7,10} True pathophysiological differences have thus remained elusive.

Differential responses to cardiovascular drugs between blacks and whites have also received widespread attention and formed part of the rationale for the FDA’s new guidelines regarding data reporting in trials: “Some differences in response to medical products have already been observed in racially and ethnically distinct subgroups of the US population. . . . For example, . . . studies have shown that blacks respond poorly to several classes of antihypertensive agents (beta blockers and angiotensin converting enzyme (ACE) inhibitors) (Exner 2001 and Yancy 2001).”² Although the FDA document refers to antihypertensive therapy as the condition of interest, the citations are studies of heart failure. Furthermore, the study by Yancy et al actually found that “(t)he benefit of carvedilol was apparent and of similar magnitude in both black and nonblack patients with heart failure.”¹¹ Furthermore, although blood pressure responses for ACE inhibitors do vary modestly among blacks and whites, there is considerable overlap, and race-specific prescribing has not been recommended in the United States.^{12,13}

Because a rigorous test of the hypothesis about racial differences in fundamental aspects of the physiology of multifactorial diseases is so difficult, the opinions advanced on this topic mainly reflect prior beliefs. Under these circumstances, there is the concern, which we share, that the idea of race can “distort, maximize and exaggerate” the nature of population differences.¹⁴ The appropriate scientific approach

is to accept the null hypothesis of no difference until convincing evidence to the contrary is available. In a highly commercialized environment such as drug development and marketing, where strong profit incentives exist, reliance on subjective judgment could have particularly unfortunate consequences.¹⁵

Two conclusions follow from these arguments. First, if after decades of intense study, we cannot resolve the issue of black-white differences in cardiovascular disease, it will be very difficult to determine what clinical syndromes are actually “unique” or “special” in any other pair of racial groups, thereby providing a mechanism for differential drug response. Second, subjective bias will play a large role in determining whether a difference is interpreted as being particularly salient. A clear mechanistic rationale would therefore be required to overcome the primary weakness of nongeneralizability that is inherent in the ethnic-specific design.

What Might Be the Role of Variation in Polymorphisms That Influence Drug Response?

Both adverse and therapeutic drug responses differ among individuals, and some of these differences are likely to be genetic.^{16,17} Sequence variations that influence bioavailability, distribution, and metabolism have also been shown to vary by race/ethnicity, although the genotype-phenotype relationships are often complex and within-race heterogeneity is large.^{18–21} Accumulating evidence suggests that these genetic variants may in turn have consequences for clinical sequelae.^{22,23} It might follow that race-specific drug responses could reflect genetic effects.

This last inference is not well founded, however. Variation at the population level is distributed differently than variation at the individual level, being graded and probabilistic rather than categorical. Furthermore, the vast majority of genetic variation (85% to 90%) is found within, not between, continental populations.^{24,25} The hypothesis that sufficiently extreme genetic variation exists between populations for ethnicity to serve as a “diagnostic marker” requires assumptions that are unlikely to be true. For group membership to be a sufficiently precise marker, the variant(s) underlying drug response must both be common and occur at very different frequencies in the 2 populations. However, common mutations tend to be old and, for that reason, widespread among regional populations.^{25–27} Between-group variation over the usual range for common drug-metabolizing polymorphisms means that racial identity will have inadequate predictive power.²⁷ For example, in the simplest case, if the prevalence of the minor allele that predicts nonresponse is 20% and 40% in 2 groups, then knowledge of group identity is associated with a boost in the likelihood of response by only 1.7 (Table). Only when the interethnic contrasts in allele prevalences reach levels of 90% versus 10%, which corresponds to likelihood ratios associated with diagnostic tests such as screening mammography, does ethnicity begin to serve as a

Framework for Assessing the Value of Ethnicity in Predicting Drug Response Based on the Presence of a Functional Allele

Ethnicity	Frequency of Response Based on Presence of Allele	
	Response	Nonresponse
Group A	80	20
Group B	60	40

Sensitivity of membership in Group A to predict response=57%; specificity of membership in Group B to predict nonresponse=66%; likelihood ratio positive=1.7.

clinically useful diagnostic predictor of potential drug response. Although possible, such a large difference in allele frequencies will be rare for large continental racial groups. The reliability of ethnicity as a “diagnostic test” would also vary depending on the available alternative treatments, the anticipated benefit, and the potential side effects. With the passage of time, as continental populations intermingle, “race” will continue to lose its predictive value as a marker for unlinked genes altogether, as has already occurred in Brazil.²⁸ Skin color and other observable traits will then be uncorrelated with the alleles that influence drug response.

Furthermore, biological variability in drug response is conditioned by a complex set of processes that involves metabolizing enzymes, receptors, signal transducers, and transporters. Because the clinical response is usually determined by the coordinated action of multiple systems, it becomes even less likely that the pattern of variation in several genes would be race-based.

On the other hand, mutations that are associated with toxic effects tend to be rare, and rare variants are more likely to be group-specific. Numerous examples now exist^{29,30}; when an adverse event is known to be much more common in one group than another, the choice of a drug or targeted screening for adverse effects could be justified in one population but not others. This distinction between the search for differential group drug response and a differential frequency of adverse drug reactions is important. Variation in low-frequency alleles responsible for adverse events cannot be used to support a general theory that groups, on average, vary in response.

There is substantial irony in the general tendency to view disease syndromes in persons of African descent as unusual or unique by virtue of nonresponse to a common therapy. Because our species evolved in Africa over millions of years, contemporary African populations retain the greatest genetic diversity.³¹ A recent analysis of 1.6 million single nucleotide polymorphisms (SNPs), for example, identified the heterozygous state in 95% of blacks compared with 81% of whites and 74% of Han Chinese.²⁵ If therefore, drug response is predicated on the presence of a specific SNP, it would be least likely for it to be absent from African-origin populations and present in all others.

In many ways, the contradiction between the evidence from genetics and the appeal of race-specific trials reflects

one of the most difficult dilemmas that we face in integrating genomics into medical practice. Racial hypotheses evoke considerable skepticism among many geneticists.^{32,33} Nonetheless, genomics has provided a new context within which racial hypotheses in medicine appear to make sense, and much of the public attention given to the issue of race-based trials incorrectly assumes that these studies are exploiting the tools of molecular science to find new therapies.^{34,35} The concept of race continues to serve as a shortcut, an imagined reality not substantiated by the scientific evidence.¹⁴ Although a proxy measure would clearly be useful, race can almost never serve as a diagnostic test for a medical condition or a common drug response. Instead of being used to reinvigorate an outmoded concept of race, pharmacogenomics should be seen as an opportunity to replace group labels with laboratory-based tests.^{16,17}

To avoid confusion on this point, we reemphasize the key points. Rare genetic variants tend to be isolated to one population.²⁵ If they are associated with toxic effects, then screening in that group alone is appropriate. However, therapeutic decisions about a class of patients based on ethnicity assume that the functional variants are present at high frequency in one population and not others. This distribution, although possible, is unlikely for common variants and cannot serve as the basis for the design of a trial unless direct genetic evidence is available. If that evidence exists, then the measurement of genetic polymorphisms in individuals, not approximate estimates based on group labels, will improve the design and power of the clinical trials.

Could Ethnicity Be a Marker for the Predominance of Clinical Subtypes?

A clear distinction can be made between the expression of a disease complex that has resulted from inherited predisposition and one that reflects the lifetime accumulation of risk factor exposure. The earlier age of onset and the higher prevalence of hypertension in blacks in the United States are probably responsible for the higher than expected rates of renal failure and stroke. Although some of the contrasts in the epidemiology of cardiovascular sequelae may be an artifact of imprecise measurement of clinical risk factors, ethnicity could be a marker for group differences in the etiology and clinical course, and as a consequence, they may predict outcomes of therapy. This scenario could then justify the focus of a clinical trial on a particular ethnic group, as the equivalent of a focus on a high-risk set of patients, and this approach was incorporated in a recent trial on renal disease among blacks.³⁶ If the hypothesis involves a differential response to drug therapy, an entirely different kind of trial, designed to evaluate effect modification by race, would be in order. As suggested above, the assumptions required for effect modification will usually be harder to justify.

What Is the Experience of Subgroup Comparisons by Ethnicity?

Ironically, the vast majority of trials conducted to date have actually been ethnic-specific. This occurred not by design but

because most trials were restricted in recruitment to a single population. The underlying assumption has been that the findings will be generalizable to other populations of whites, blacks, Asians, etc. In practice, the possibility of differential responses has been generally ignored, although recent guidelines stipulate conditions under which “bridging trials” would be required to introduce drugs into new populations in which no experimental data have been collected.³⁷ Dosing and adverse response rates are the most likely factors to vary, and for most classes of cardiovascular drugs, there has been little difficulty extrapolating from one population to another. Other ethnic-specific trials are ongoing, although the scientific justification is not always clear.³⁸ In any case, the conduct of ethnic-specific trials to get physicians’ attention for marketing purposes is not appropriate.

The best source of information on ethnic-specific responses is therefore data from existing trials. Attempts to extract information regarding ethnic subpopulations confront a number of obstacles, however, including the hazards of multiple testing. Undue emphasis can be given to the post hoc interpretation of differential response by race, especially when a large number of secondary end points are examined.^{39–41} Because the test of a significant difference between groups is based on a test for interaction, 4 times the sample size of a simple exposed versus unexposed comparison is generally required to achieve similar power.⁴² Rarely do trials have the luxury of 4-fold overrecruiting beyond the primary aims. In the absence of strong statistical evidence of an interaction, the best evidence about a drug effect in a subgroup is the evidence from the trial as a whole. In the absence of prespecified hypotheses about race differences, it is therefore uncommon to be able to make claims about ethnic-specific effects with the same degree of certainty as applied to the main end points. A major exception is ALLHAT, in which tests of ethnic effects were specified in advance.^{1,30} Although they confirmed small differences in achieved blood pressure reduction with an ACE inhibitor, ALLHAT investigators concluded that initial therapy for hypertension should be the same for both blacks and whites.³⁰ ALLHAT therefore answered the specific question about the optimal first-line drug for the pharmacological treatment of high blood pressure. This approach, when feasible, is clearly preferable to ethnic-specific studies. We recognize, of course, that trials of this magnitude are very expensive and alternative approaches may be required to move the process of drug evaluation forward.

Having Said That, What About AHeFT?

AHeFT enrolled self-identified African-Americans with New York Heart Association class III and IV heart failure in a trial of the addition of isosorbide dinitrate and hydralazine to standard therapy with ACE inhibitors and β -blockers.³ The benefit documented in AHeFT was as large as the observed benefit in single-therapy trials of ACE inhibitors and β -blockers.^{3,43} The evidence for a differential response by

race before AHeFT was not particularly robust, however. The previous trials with similar agents failed to show a significant interaction by race, and a meta-analysis of β -blocker and ACE inhibitor trials found identical benefit in blacks and whites, with the exception of Beta-Blocker Evaluation of Survival Trial (BEST).⁴³ In SOLVD (Studies Of Left Ventricular Dysfunction), the only ACE inhibitor heart failure trial with sufficient numbers of blacks and whites, no difference in the primary outcome was noted, and post hoc analyses of secondary end points were inconsistent with regard to differential racial effects.^{40,41} In ALLHAT, the relative outcome for heart failure for a diuretic versus an ACE inhibitor in blacks and whites was indistinguishable, before and after control for blood pressure effects.³⁰ Because only blacks were enrolled in AHeFT, it provides no direct evidence on differential efficacy. A similar group of patients from any ethnic background could potentially respond as well. Unfortunately, the hypothesis of a differential response, with which the trial design began, remains untested. The results of AHeFT provide no evidence to justify a change in the basic principles of randomized trials.

Conclusions

The conduct of science creates all sorts of new observations, some expected and some unexpected. In either case, we can err by being too accepting of the evidence or too skeptical. This decision is more difficult when we are confronted with information that does not conform to our prior expectations, and the overly rigid adherence to principles is thereby an important threat to the acceptance of new knowledge. Until now, the guiding principle for trial recruitment has been diversity. However, genomics is providing unexpected new insights into biology at a rapid rate, and there is no reason to believe that it might not change clinical epidemiology and the design of trials as well.

However, the idea that the conduct of trials would be enhanced if they were restricted by ethnicity should evoke skepticism. Presently, all major classes of drugs work in all ethnic groups, albeit with notable differences in minor frequencies of adverse or blunted responses. The demonstration of efficacy in trials that by design enroll only 1 ethnic group does not serve as the basis for overturning the well-established principle of inclusiveness and diversity. The justification based on genetics is not well founded, and important nongenetic traits of patients should be measurable. The trend toward diversity as the guiding principle in recruitment should be maintained and expanded. When necessary, sufficient numbers of patients can be recruited to provide adequate power for subgroup analyses for which there are reasonable biological hypotheses. A clear mechanistic rationale might help overcome the primary weakness of this design, which will be nongeneralizability.

Prior history of the use of race in biomedicine in America suggests that we will remain deeply confused about how to define it and how to interpret its significance.⁴⁴ The wide-


spread news coverage of AHeFT suggests that a similar response lies in wait for ethnic-specific trials.^{34,35,38} Racial theories and racially exclusionary policies in the long run have never been beneficial for ethnic minority groups.⁴⁵ We would be better served to use unambiguous traits and clinical measurements as the basis for entry criteria rather than race/ethnicity.

Disclosures

None.


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Response to Cooper and Psaty


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There is substantial agreement between Drs Cooper and Psaty and ourselves. We both agree on the importance of “including diverse groups of patients in adequate sample sizes to test for differential response” and that ethnic-specific trials should be supported by a theoretical rationale. These criteria apply to A-HeFT, AASK, and

ALLHAT. We also agree that the best source of information on ethnic-specific responses is data from existing trials, but we point out the unfortunate paucity of such data.

We agree that a disease complex may result from both inherited predisposition and lifetime risk factor exposure. However, these 2 factors are often intermingled within a




population described by ethnicity/race. Thus, ethnicity/race may serve to identify a high-risk population even in the absence of clarity regarding the precise mechanism responsible for differential risk. Pharmacogenomics may, in the future, represent a more precise approach to identify drug responsiveness; however, as we both note, genetics is unlikely to explain all differences in subgroups. Thus, we restate the value of investigation of population differences.

We strongly disagree with Drs Cooper and Psaty's interpretation of the ALLHAT outcomes. It is true the ALLHAT

investigators concluded that initial therapy for hypertension (thiazide diuretics) should be the same for both blacks and whites; however, the magnitude of differences in effect between angiotensin-converting enzyme inhibitors and diuretics in blacks (but not in whites) was sufficiently large that it was concluded that angiotensin-converting enzyme inhibitors should be considered secondary antihypertensive therapy in blacks. Finally, the objective of A-HeFT was to confirm previous retrospective observations rather than to test for differential efficacy by race.

Response to Taylor and Wright

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We agree with Taylor and Wright that trials such as AASK, ALLHAT, and AHeFT have made important contributions, although we differ perhaps in interpretation. In ALLHAT, several treatments were compared in large samples of blacks and whites. This approach made it possible to identify potential interactions between treatments and factors such as ethnicity and provided clinically useful information, namely, that first-line therapy should be the same. In AASK, blacks with renal insufficiency were targeted for enrollment because of their high risk of end-stage renal disease. This approach is similar to enrolling high-risk subjects defined by age, sex, or other risk factors. Several active treatments were used, and the effects were compared, which again demonstrated the efficacy of standard therapy in blacks (ie, angiotensin-converting enzyme inhibitors). In AHeFT, however, blacks were targeted for enroll-

ment because they were hypothesized to be especially responsive. The prior evidence for this hypothesis was suggestive but not compelling. In particular, we believe it is incorrect to argue that angiotensin-converting enzyme inhibitors have been shown to be less effective in heart failure in blacks; in SOLVD, the only large trial, the outcome for the primary trial end point was identical. Subsequently, although AHeFT showed a clear benefit, the limitations of the trial design leave unanswered the question of whether the response actually differs between whites and blacks. These examples are consistent with our more general argument that race-specific trials have a very limited role based on the difficulty of obtaining reliable prior evidence, an absence of clinical rationale, and the lack of generalizability. These difficulties are avoided with trials like ALLHAT and SOLVD.